

DO NOT CIRCULATE

VOLUME 46 NUMBER 4

APRIL 1953

UNIVERSITY
OF MICHIGAN

MAY 25 1953

✓ MEDICAL
LIBRARY

PROCEEDINGS

of the

ROYAL

SOCIETY OF MEDICINE



Published for

THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W.1

by

H. K. LEWIS & Co. LTD., 136 GOWER STREET, LONDON, W.C.1

In U.S.A., GRUNE & STRATTON, INC., 381, FOURTH AVENUE, NEW YORK CITY

Monthly, 10s. 6d. net Annual Subscription, £6 6s. in the British Commonwealth,
\$19.00 in the U.S.A.

All rights reserved

ORAL IRON



FERRIVENIN

Trade Mark

for **IRON DEFICIENCY**

ANÆMIA

during **PREGNANCY**



Benger Laboratories

To achieve a satisfactory response to oral iron therapy, it is often necessary to administer iron **ad nauseam**, since maximum utilization by this route is only 14%. This figure is further reduced when there is impaired gastro-intestinal absorption or intolerance — not uncommon in pregnancy.

Intravenous iron therapy with FERRIVENIN is a safe and effective means of ensuring 100% utilization resulting in an immediate rise in the haemoglobin level. FERRIVENIN is especially indicated when iron-deficiency anaemia is diagnosed during the third trimester.

PROCEEDINGS of the ROYAL SOCIETY OF MEDICINE

ISSUED UNDER THE DIRECTION OF THE EDITORIAL COMMITTEE

HONORARY EDITORS

E. R. CULLINAN

SIR HENEAGE OGILVIE

EDITOR

M. BROWNE KUTSCHBACH

ROBERT COPE (Anaesthetics)

FRANCES GARDNER (Clinical)

J. B. BROOKSBY (Comparative Medicine)

D. I. WILLIAMS (Dermatology)

E. F. SCOWEN (Endocrinology)

IAN TAYLOR (Epidem. & Preventive Med.)

A. C. WHITE (Exper. Med. & Therap.)

L. CARLYLE LYON (General Practice)

H. M. SINCLAIR (History of Medicine)

W. A. MILL (Laryngology)

MAURICE DAVIDSON (Medicine)

J. W. ALDREN TURNER (Neurology)

LESLIE WILLIAMS (Obstetrics and Gynaecology)

B. W. FICKLING (Odontology)

FREDERICK RIDLEY (Ophthalmology)

R. C. F. CATTERALL (Orthopaedics)

R. SCOTT STEVENSON (Otolary)

D. MacCARTHY (Paediatrics)

F. R. SELBIE (Pathology)

W. S. TEGNER (Physical Medicine)

RONALD W. RAVEN (Proctology)

GERALD GARMANY (Psychiatry)

F. CAMPBELL GOLDING (Radiology)

CHARLES DONALD (Surgery)

Surg. Cdr. J. L. S. COULTER (United Services)

A. CLIFFORD MORSON (Urology)

SECRETARY OF THE ROYAL SOCIETY OF MEDICINE

R. T. HEWITT

All communications concerning Editorial Business should be addressed to
THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1 (Tel.: LANGHAM 2070)

A new Sandoz preparation . . .

HYDERGINE

for the treatment of

HYPERTENSION and PERIPHERAL VASCULAR DISORDERS

Five years of extensive clinical trials have demonstrated that **HYDERGINE**, a combination of 3 hydrogenated ergot alkaloids (dihydroergocornine, dihydroergocristine, dihydroergokryptine), alleviates subjective complaints and lowers blood pressure in hypertension, increases blood flow in the extremities and dilates the collateral vessels in severe obliterative disease. No undesirable side effects have been reported so far.

Full details available on request

TABLETS for sublingual or buccal administration

AMPOULES for subcutaneous, intramuscular and intra-arterial injection



SANDOZ PRODUCTS LIMITED

134, Wigmore Street,

London, W.1

The professional touch . . .

There is that about the Jaguar which recommends it at once to the man of professional calling, and some measure of the high appreciation it inspires can be gauged from the frequency of its appearances in professional and diplomatic circles, not only in this country but throughout the world.

JAGUAR



JAGUAR CARS LTD., *Coventry, England*
London Showrooms: HENLYS LTD.
Devonshire House, Piccadilly, W.1

Grace . . . Space . . . Pace

PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE

Vol. 46 No. 4 April 1953

CONTENTS

	Whole Proceedings Page
Section of Radiology	
Experience with Two Million Volt X-ray Therapy and a Preliminary Assessment of Clinical Results.—G. W. BLOMFIELD, M.A., F.R.C.S., M.R.C.O.G., D.M.R. . .	219
Section of Neurology	
DISCUSSION ON THE USE OF ISOTOPES IN NEUROLOGY	225
Section of Surgery	
DISCUSSION ON THE USE OF RADIOISOTOPES IN SURGERY	233
Section of Experimental Medicine and Therapeutics	
DISCUSSION ON THE RADIATION SYNDROME	245
Section of Pathology	
SYMPOSIUM ON THE BASIS OF ALLERGIC REACTIONS	253
Section of Ophthalmology	
DISCUSSION ON THE ASSOCIATION OF EYE AND SKIN DISEASES	265
Section of Paediatrics	
Endocardial Fibro-elastosis in One of 3-year-old Twins.—J. J. KEMPTON, M.D., M.R.C.P.	271
Periarthritis Nodosa.—S. D. V. WELLER, M.D., M.R.C.P.	274
Peripheral Vascular Disease in a Child.—ROBERT WIGGLESWORTH, M.B., M.R.C.P. (for VICTORIA SMALLPEICE, M.D., F.R.C.P.)	275
Eosinophilic Granuloma of Skin.—N. R. BUTLER, M.D., M.R.C.P., and M. GARRETT, M.R.C.P. (for BERNARD SCHLESINGER, M.D., F.R.C.P., and P. J. HARE, M.D., M.R.C.P.)	276
Letterer-Siwe Disease Controlled by Cortisone.—P. J. N. COX, B.M., M.R.C.P. (for Professor A. A. MONCRIEFF, C.B.E., M.D.)	278
Turner's Syndrome with Coarctation of the Aorta.—D. G. VULLIAMY, M.D., M.R.C.P.	279

Continued overleaf

THE TREATMENT OF oro-pharyngeal infections

'PONDETS'

A unique presentation of penicillin for the treatment of minor superficial oro-pharyngeal infections.

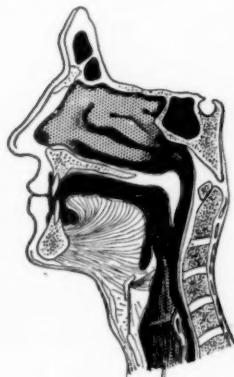
The ingenious and novel method of presenting penicillin in 'Pondets,' enables a high therapeutic concentration to be maintained in the immediate vicinity of the oro-pharyngeal mucosa, for a prolonged period.

Each 'Pondet' contains 5,000 units of crystalline penicillin-G in a pleasantly flavoured, hard, fruit-sweet base, which dissolves slowly in the mouth.

'Pondets' are indicated for all minor superficial oral infections due to penicillin sensitive organisms.

Individually wrapped in bottles of 20.

'Pondets' PENICILLIN TROCHES
Trade Mark



JOHN WYETH & BROTHER, LTD., CLIFTON HOUSE, EUSTON ROAD, LONDON, N.W.1.

CONTENTS (<i>continued</i>)		Whole Proceedings Page
Section of Epidemiology and Preventive Medicine		
Acute Epiglottitis (Acute Supraglottitis).—FRANCIS E. CAMPS, M.D.		281
Section of Dermatology		
<i>October 16, 1952</i>		
Case for Diagnosis. ? White Sponge Nævus of the Mouth.—R. P. WARIN, M.D. M.R.C.P.		285
Poikiloderma Congenitale (Thomson).—C. H. WHITTLE, M.D.		285
Miliary Lymphocytoma of the Face.—E. WADDINGTON, M.D., M.R.C.P.		286
List of Other Cases Shown		288
<i>November 20, 1952</i>		
Dermatomyositis.—J. R. SIMPSON, M.R.C.P.		288
Onchocerciasis.—K. D. CROW, M.R.C.P., and R. H. SEVILLE, M.D.		289
List of Other Cases Shown		290
Section of Endocrinology		
<i>October 22, 1952</i>		
DISCUSSION ON THE PHYSIOLOGY AND CLINICAL DISORDERS OF THE PARATHYROID GLANDS		291
<i>November 26, 1952</i>		
Male Pseudohermaphroditism.—C. N. ARMSTRONG, M.D., F.R.C.P., D.P.H.		301
Vitamin-D Resistant Osteomalacia Associated with Neurofibromatosis.—B. E. C. NORDIN, M.D., and RUSSELL FRASER, M.D., F.R.C.P.		302
Cushing's Syndrome Due to Adrenal Cortical Tumour.—J. M. STOWERS, M.R.C.P. (for Professor M. L. ROSENHEIM, F.R.C.P.)		304
Hypoparathyroidism Complicated by Impetigo Herpetiformis.—D. G. FERRIMAN, D.M., M.R.C.P.		305
Functioning Malignant Islet-Cell Tumour of Pancreas. Primary Growth Removed, Metastases in Liver Seen. Recurrence of Hyperinsulinism, Treated with Cortisone.— A. STUART MASON, M.D., M.R.C.P.		305

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Copyright: The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors. All papers, &c., presented at meetings (other than those which have been previously published) are held to be subject to the Society's copyright until a decision in regard to their publication has been made.

If aspirin were freely soluble and bland—
If calcium aspirin were stable and palatable—
That would be Solprin

'Solprin' provides pure calcium aspirin; yet is in stable, palatable tablet form. It thus overcomes the disadvantages of aspirin, low solubility and acidity, and the defect of calcium aspirin, a liability to decomposition during manufacture and storage. And it thus combines the analgesic, sedative and anti-rheumatic uses of aspirin with the ready solubility and blandness of pure calcium aspirin.

SOLPRIN *stable, soluble, palatable calcium aspirin*

EMOD.

Clinical sample and literature supplied on application. Solprin is not advertised to the public and is available only on prescription (U.K. and Northern Ireland only). Dispensing pack, price 7/6 (Purchase Tax Free) contains 300 tablets in foil.

BECKITT & COLMAN LTD., HULL AND LONDON. (PHARMACEUTICAL DEPT., HULL)

Section of Radiology

President—CONSTANCE A. P. WOOD, M.A., M.R.C.P., F.F.R.

[November 21, 1952]

Experience with Two Million Volt X-ray Therapy and a Preliminary Assessment of Clinical Results

By G. W. BLOMFIELD, M.A., F.R.C.S., M.R.C.O.G., D.M.R.

THE production of very high voltage X-rays for therapy is now a practical possibility, limited mainly by the expense of installing the equipment and running it.

It is a long way from the drawing board to the construction and installation of practical equipment responding to the controls. It is also a long time before series of cases can be collected of sufficient number on a stabilized technique for analysis. It takes a further period of years before the survival results of cancer cases treated on these techniques can be of statistical significance. In Sheffield we have had the use of a two million volt X-ray generator for three years only, and it is still very early to talk about survival results.

ADVANTAGES OF HIGH VOLTAGE IRRADIATION

Going up the energy scale from orthodox 200/250 kilovolts for deep X-ray therapy, there is a very gradual alteration in the physical characteristics requiring a very considerable rise in energy to effect comparatively small changes in penetration. So much is this the case that it is not until the million or two million volt level is reached that any considerable gain is achieved. Two million volt X-ray really does begin to make a difference, and provides something economically possible and practical in between the present orthodox X-ray equipment and the betatrons and synchrotrons or linear accelerators in the ten to fifty million volt range. It is also similar to what we would get out of a high output cobalt unit.

THE VAN DE GRAAF GENERATOR

The Van de Graaf Generator was the most economic answer at the time we ordered our machine in 1946, and two million volts was the practical economic limit to such a machine being mobile. So we decided on the 2 MeV level, the radiation of which is intermediate between conventional deep X-ray therapy and the ultra-high voltage.

Physical factors which interest us particularly are:

- | | |
|--|--------------------------------|
| (1) Quality of radiation. | |
| (2) Build up | } Together dependent upon (1). |
| (3) Penetration | |
| (4) Isodose distribution for different fields. | |

At the same time the practical possibilities of making use of these factors clinically depend upon mechanical and electrical qualities of the machine to an extent soon apparent to anyone dependent upon one single unit. To wit:

- (1) Reliability.
- (2) Output.
- (3) Manœuvrability and ease of control.
- (4) Ease of servicing and replacement of parts.
- (5) Accuracy of beam definition.

There are other factors, such as economy of operation, which should not be lost sight of.

CLINICAL ASSESSMENT

The value and advantages of 2 MeV radiation must ultimately be based upon practical experience, and a great many things come into the picture. Survival statistics, for which considerable time is required, with comparable control series, are regarded by many as the acid test of efficacy. Other things for which we may not have to wait so long can be assessed sooner. Treatment without "high dose effects"—generally referred to by our medical and surgical colleagues as "radiation burns" or "radionecrosis"—is of great importance, and the general relief or control of disease without severe cutaneous reactions or nauseating radiation sickness is a great benefit.

The avoidance of tedious treatment, with long sessions under the X-ray and multiple fields, which many ill patients cannot stand, is also a great boon to the patient and a great convenience.

EXPECTED GAINS

Returning to expected gains from physical factors, let us consider skin and mucosal reactions.

The clinical effect is about what could be expected, assuming that the basal-cell zone of the skin is the most important structure in the mechanism of skin reactions. Skin reactions are not wholly predictable with orthodox radiation, and one finds that certain sites are far more susceptible than others. Irritating discharges have aggravating effects, and trophic skin changes will make the skin sensitive to any injury, physical or otherwise. To give typical examples of reactions to the 2 MeV radiation which are visible—a skin dose of 4,000 r over the pelvis, made up of 3,000 r incident and 1,000 r from the opposite side, fractionated to five doses per week for four weeks, will give a mild erythema only, with a more marked reaction over the pubes. This is with 15×15 cm. fields to cover a substantial area; smaller fields will give less reaction. Where, however, the radiation glances and touches the skin tangentially, or where there is a fold taking the skin into the depth of the tissues, there will be more marked reaction; in fact the skin reaction is then what one would expect with full "build up" and approaches the reaction obtained at the same dose with conventional deep X-ray.

As a fairly good test of the build-up effect, we have observed and compared reactions on the incident and exit sides, using a single field on the limb or neck. In treatment of the larynx by a single field 6×8 cm., the skin reaction at the opposite side of the neck is roughly the same as over the incident side. An exit dose of 3,000 r, given in four weeks, results in a slight to moderate erythema similar to that caused by an incident dose of 5,000 r. The gain in depth dose is greatest for small fields and for considerable depth. This is due to greater penetration and forward scatter. Side scatter is less and the tumour area can be covered with greater accuracy than with conventional methods provided the aim is accurate. Table I shows build-up and penetration for small and medium-sized fields. 200 kV. X-ray is shown in adjoining columns for comparison. Fig. 1 shows two comparable fields, at 2 MeV and at 200 kV.

TABLE I.—SHEFFIELD NATIONAL CENTRE FOR RADIOTHERAPY
CENTRAL AXIS DEPTH DOSES AT 200 kV. AND 2 MeV

Depth (cm.)	6 × 8 cm.		10 × 10 cm.		20 × 20 cm.	
	2 MeV (HVL 6.8 mm. Pb) 70 cm. F.S.D.	200 kV. (HVL 1.5 mm. Cu) 50 cm. F.S.D.	2 MeV (HVL 6.8 mm. Pb) 70 cm. F.S.D.	200 kV. (HVL 1.5 mm. Cu) 50 cm. F.S.D.	2 MeV (HVL 6.8 mm. Pb) 70 cm. F.S.D.	200 kV. (HVL 1.5 mm. Cu) 50 cm. F.S.D.
0	28	100	34	100	45	100
0.05	60		64		72	
0.1	77		79		85	
0.2	90		91		95	
0.4	100		100		100	
0.6	102		102		100	
0.8	101		101		100	
1.0	100	97	100	99	100	101
2.0	94	87	95	91	96	94
3.0	88	77	90	82	91	88
4.0	82	68	84	73	86	82
5.0	76	59	78	65	81	76
6.0	71	51	73	58	77	69
8.0	60	39	63	44	68	57
10.0	50	29	54	34	59	47
15.0	33	15	36	18	43	28
20.0	21	7	24	10	31	16

MUCOSAL REACTIONS

Mucosal reactions at depth give us a fair assessment of the biological effect. Mouth, pharynx and larynx cases have been carefully observed by all of us at Sheffield, and the actual clinical reaction of the mucosa in mouth, pharynx and larynx differs but slightly from reactions obtained with radiation at 200 kV., and comes on at a slightly higher dose level. There is of course no "build up" here unless the patient is given a direct beam through the open mouth. We have found that 6,000 r units given to the mucosa, such as in the treatment of carcinoma of the larynx, in an overall time of five weeks, gives rise to reactions very similar to what we find at 5,000 r units in the same overall time at 200 kV.

BEAM DEFINITION

As judged by the clinical reactions, the cut-off, using tungsten blocks at 35 cm. and a 70 cm. Focal Skin Distance, is quite as accurate as it is with orthodox radiation. For such special work as treating

the posterior hemisphere of the eye by a lateral field, special inserts can be used which enable smaller fields to be accurately defined.

As regards Focal Skin Distance, isodose distribution charts show that 70 cm. F.S.D. is ideal for routine work. For large cross sections and for extreme thicknesses between opposed surfaces, 100 cm. F.S.D. may be necessary. For rotational therapy an increased distance will be necessary for clearance purposes, and for very large fields the usual long distances are of no detriment as treatment times will still be short.

CLINICAL RESULTS

In planning our programme of clinical work the order of things has been:

(1) Physical investigations for six months, during which the general performance of the machine was tuned up.

(2) A period of six months or so on a combined programme of physical and clinical work.

The clinical programme commenced in December 1949, and for the purpose of reviewing the work I have taken all the 1950 cases. These have been followed up on an average for a period of just over two years. This will not give very much statistical weight on survival times, but it has left me with very definite impressions on how the patients fared.

One general impression of some significance is that patients are not frightened by these machines.

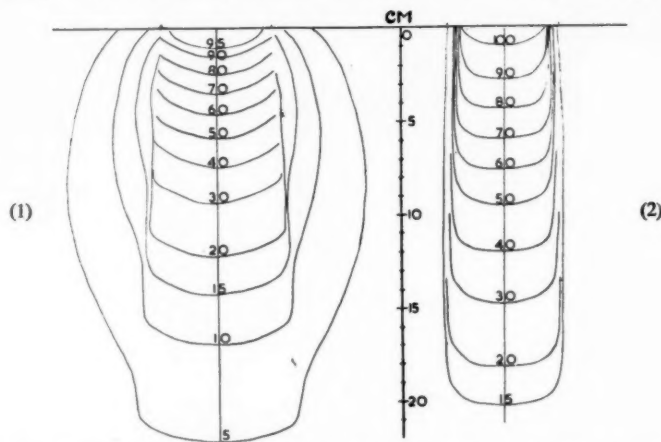


FIG. 1.—Two X-ray isodose charts for single field, 6 cm. wide \times 8 cm.: (1) 200 kV, 40 cm. F.S.D.; (2) 2 MeV 70 cm. F.S.D.

So long as they are properly handled by the staff they have immense confidence and they very much prefer a machine which is not touching the person, i.e. without applicators pressing upon them.

The total number of cases treated in the two-year period (December 1949 to December 1951) was 749.

Table II gives the classification of the chief series included.

Diagnosis		TABLE II		No. treated	
1	Intracranial tumours	62	(12 of these non-malignant)
2	Carcinoma mouth (tongue, alveolus, antrum, palate, &c.)	65	
3	Carcinoma larynx	30	
4	Carcinoma oesophagus	16	
5	Carcinoma bronchus and lung	39	
6	Carcinoma rectum	20	
7	Carcinoma bladder	65	
8	Carcinoma cervicis uteri	227	
9	Artificial menopause	79	
10	Other cases	146	
				749	

Intracranial tumours.—There are obvious advantages in using supervoltage X-ray therapy as opposed to conventional deep X-ray for intracranial tumours, and almost all our cases were referred from the Neurosurgical Department, mostly after an incomplete removal. Of 20 cases treated in 1950 and 2

cases of chromophobe adenoma of the pituitary gland, 9 were alive up to October 1952. These included 3 cases of meningioma, 2 cases of ependymoma, one case of hæmangioblastoma and one case of medulloblastoma. An isodose chart for a multiple field treatment is shown, Fig. 2. A beam direction technique is illustrated in Fig. 3.

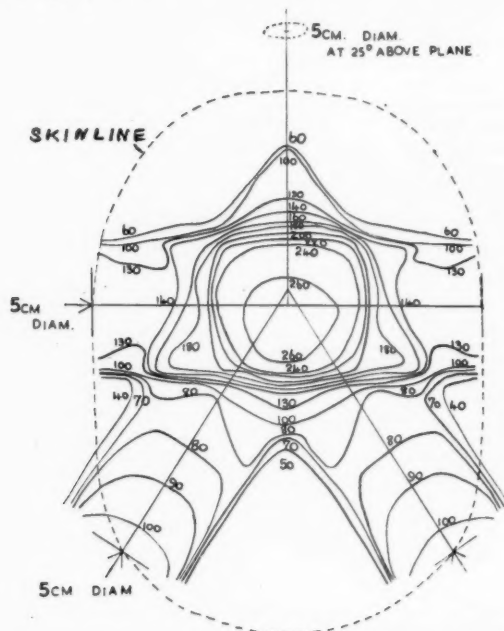


FIG. 2.—Isodose distribution for five fields, directed to pituitary fossa.



FIG. 3.—A beam direction technique for head cases.

Mouth cases.—The mouth cases treated were mostly difficult ones unsuitable for radium or ordinary techniques, such as carcinoma involving the mandible and with secondary glands of the neck. Good survival results could not be expected on this account, but some individual cases did well. An example is illustrated, before and after treatment (Figs. 4 and 5).

Carcinoma of larynx and pharynx.—A single field would serve well for an intrinsic growth without secondary glands, but we have generally found it advisable to be more radical and use two opposed fields. These can be wedged by lead filters to give a uniform through and through dose. As we are now using the cobalt beam for early cases the tendency has been to reserve supervoltage for the more extensive ones where considerable advantage is likely to be gained.

Carcinoma of œsophagus.—Of 9 cases treated in 1950 one survived for nearly two years and died

cluded
case of
ection

from secondary extensions. Palliation was good in all cases well enough to receive a full course of treatment.

Malignant tumours of the bladder.—There are very great advantages to be obtained by using super-voltage X-ray therapy as opposed to conventional deep X-ray for treatment of inoperable tumours of the bladder. The two isodose charts shown in Fig. 6 will give evidence of this. Accurate localization is necessary and this is done both from the front and from the back by tube shift, the two halves



FIG. 4.



FIG. 5.

Figs. 4 and 5.—Carcinoma of floor of mouth involving mandible, Fig. 4 before, and Fig. 5 after treatment by 2 MeV (two fields).

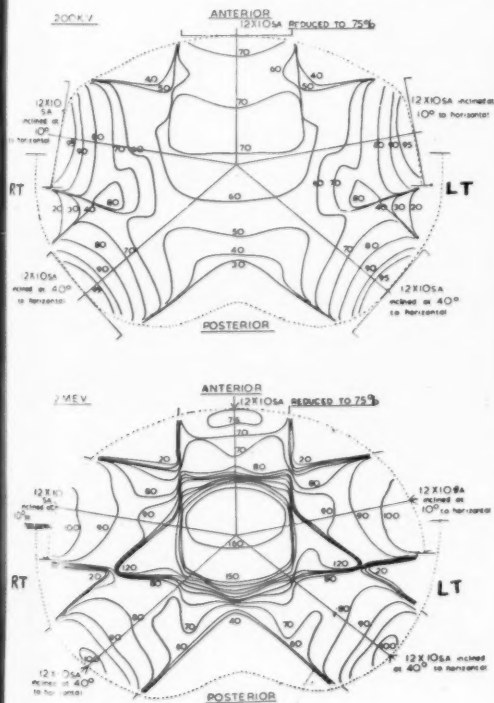


FIG. 7.—Lead filter for blocking out centre of field; supplementary irradiation treatment for carcinoma of cervix.

← FIG. 6.—Isodose distribution for 5 fields directed to tumour of bladder: (1) 200 kV. 40 cm. F.S.D.; (2) 2 MeV 70 cm. F.S.D.

being plotted separately and joined together with the tumour level correct for each. Of a total of 26 cases treated in 1950, 11 are alive and well and the living include some cases of extensive growth treated by supervoltage X-ray therapy alone.

Carcinoma of bronchus.—We have not attempted to treat many lung cases. Of 14 treated in 1950 one carcinoma of bronchus is alive (24.10.52) with a recurrence.

Carcinoma of rectum.—14 cases were treated in 1950 with inoperable growths of the rectum. Good palliation was obtained. 10 died within one year and one has died since. 2 are alive with persistent growth two years after treatment.

Artificial menopause.—This non-malignant series was included as a matter of policy and also to test for the gamma ray dose necessary to produce artificial menopause by external irradiation. The treatment has usually been given as a single dose of 350 to 450 r to the mid-pelvis, by two opposed fields 15×15 cm. The bigger dose is given to the younger patients. The single treatment has proved almost 100% effective so far and appears to be sufficient. For obese patients with a deep pelvis it has been better policy to fractionate a larger dose, and anything above 400 r through the pelvis in a single treatment is liable to cause an undesirable intestinal reaction in a proportion of cases. This reaction clears up quickly but can be severe whilst it lasts.

Carcinoma of uterine cervix.—This series is one of importance and interest. The policy has been to treat all cases of carcinoma of the uterine cervix with supplementary supervoltage X-ray therapy in addition to the radium treatment, and some stage 3 and stage 4 cases were treated by external irradiation alone. Of 112 cases treated in 1950, 55% were alive up to October 31, 1952. The supplementary radiation was given to raise the dose to Point B¹ up to 3,500 r total in the early cases and up to 4,000 r or 4,500 r or even to 5,000 r in the more advanced cases where there was clinical evidence of spread to the parametrium or to pelvic glands. The method by which this is now done is by two opposed fields suitably blocked in the middle, using a lead filter graded off at the parallel edges. This filter was omitted when radium was unsuitable in the very advanced cases. When in use it is attached by two magnets and adjusted by the optical field-defining device (Fig. 7).

We have found this a very simple and convenient way of giving the radiation, and in the course of time we should have a statistically significant series to compare with the previous years when conventional deep X-ray therapy was used. We have not had any appreciable complications and have been significantly free from such grave complications as recto-vaginal and vesico-vaginal fistula. We have found it desirable to take the dose up at the rate of 800 to 1,000 r per week to the pelvic wall.

Miscellaneous cases.—A number of miscellaneous cases, such as breast tumours presenting special problems, ovarian tumours and soft tissue sarcomas, have been treated. It has not been possible to include breast tumours as routine cases owing to their number and the time which would be necessary, but it is well worth including such cases if apparatus is available.

Conclusion.—The experience of the past three years, during which time we have used the 2 MeV machine, leaves me in no doubt that the change to supervoltage X-ray therapy for the treatment of deep-seated cancer, and indeed certain other cancers and lesions, is as well justified as the change from 150 kV. to 200 kV. X-radiation which took place about twenty years ago. There is, as ever, the necessity for accurate localization and direction of treatment, but the ease with which the treatment can be administered and the almost complete elimination of severe skin reactions, combined with the gain in accurate delivery of the radiation where it is required, is an immense advantage.

Mr. G. R. Newbery asked the speaker to comment on the possible value of supervoltage X-ray therapy and to inform the meeting of the techniques he has used or intends to use, in the treatment of carcinoma of the breast.

Dr. N. S. Finzi said that at St. Bartholomew's Hospital a slight but quite definite improvement in results was found when the voltage was raised to a million and this occurred not only in deep growths, but also in relatively superficial growths such as maxillary antrum, thus indicating a change in the biological value of the shorter wave-length X-rays. The preliminary results described in this discussion seemed to indicate that this improvement was carried further with the increased voltage. He noted that the very poor output of the synchrotron limits greatly the number of cases that can be treated. St. Bartholomew's had on order a linear accelerator to work at 15 million volts. Shouldn't this give a considerably higher output than the synchrotron?

Dr. G. Spiegler remarked on a similarity between the dose distribution obtained from the synchrotron and that achieved with 200 kV. by the technique of convergence therapy, in which the tube focus describes a spiral movement on the surface of a spherical cap, a method used by Nielsen (Copenhagen) and by Wachsmann and Barth (Erlangen).

Mr. G. W. Blomfield, in reply to Mr. Newbery, said that breast cases could not be included as routine but a limited number of breast cases were treated and very considerable advantage was obtained over orthodox techniques by virtue of the better depth-dose delivered to the axillary and supraclavicular glands. He used beam-directed glancing fields for the breast and treated the axillary and supraclavicular glands by two opposed fields, delivering a depth dose of 5,000 r units in four weeks.

¹The Point B referred to is defined as 5 cm. lateral to the mid-line of the uterus and 2 cm. above the vaginal vault. It is near the pelvic wall.

Profess

Intro

in the

but the

of the f

salutary

expect t

(Types

attack

With

in very

material

each ma

rate. T

material

Na²⁴ en

rays of

or xeno

in diagn

With

compos

and pat

hope to

the radi

to the a

detection

our estim

active m

I leave

isotopes

If a ra

depends

of conce

these qu

ment of

of radio

I will

a wide r

proteins

from the

perilymp

Metho

of the ra

Let us

specimen

"liquid c

the liqui

and by s

the conte

geometry

sensitive.

An int

consists

now cont

and is pa

terphenyl

Each bet

APPEND

Section of Neurology

President—MACDONALD CRITCHLEY, M.D., F.R.C.P.

[January 8, 1953]

DISCUSSION ON THE USE OF ISOTOPES IN NEUROLOGY

Professor W. V. Mayneord:

Introduction.—Several centres in this country have now had some five or six years of experience in the use of the new radioactive materials. Very interesting and useful years they have proved, but the time has arrived when we may begin to see, not only some of the possibilities but also some of the fundamental limitations of their use. I propose, therefore, to devote some of my time to this salutary, even if somewhat depressing, task of discussing what we may not, as well as what we may, expect to be able to do.

Types of problems.—Let us therefore look at the kinds of problems we may expect to be able to attack by using radioactive isotopes.

With the possible exception of tritium, the metabolism of the radioactive materials, if administered in very small amounts, is exactly the same as that of their non-active counterparts. The radioactive materials emit alpha, beta or gamma rays over a wide range of energies and, therefore, penetrations, each material emitting a characteristic radiation and decaying exponentially at an equally characteristic rate. The alpha ray emitters are few and of little interest so that we have, in practice, to deal with materials such as P^{32} , emitting pure beta radiation travelling only a few millimetres in soft tissues, or Na^{24} emitting both penetrating gamma rays and beta rays; I^{131} again emits a mixture but gamma rays of much less penetration. Recently I have found much interest in such materials as thulium¹⁷⁰ or xenon¹³³ which emit gamma rays of so low an energy as to simulate the low voltage X-rays used in diagnosis.

With suitable detectors we may therefore study the metabolism of particular elements (or stable compounds containing them) in the body, and use such studies to scrutinize and compare normal and pathological processes. By introducing much larger amounts of the same materials we may hope to influence metabolism, as for instance the growth of malignant cells, and thus make use of the radioactive substances therapeutically. In the first instance the amount of material administered to the animal or patient will be as small as possible and limited by the sensitivity of the means of detection. In the second, the amount may be thousands of times larger and often, I fear, limited to our estimate of the maximum amount we dare to give, since, in general, the concentration of radioactive material in the tissue to be treated is barely sufficient.

I leave aside deliberately the interesting possibilities of use of large extended sources of radioactive isotopes after the manner of an X-ray tube and continue with the problem of internal administration.

If a radioactive material be administered to a patient, the physical problem upon which all else depends is its distribution in the body, depending upon the natural history of the material, its degree of concentration in various tissues, cells or parts of cells, its rate of excretion and the variation of these quantities with time. Our own interests lay particularly in the localization and possible treatment of tumours of the brain and it was natural therefore to study by various methods the amounts of radioactive materials taken up in these tissues.

I will discuss these applications in particular, but radioactive isotopes have already been used in a wide range of experimental work in neurology, as for example studies of the spread of radioactive proteins in the nervous system of rabbits, studies of the penetration of sodium and phosphate ions from the plasma into regions of active nerve tissue, or investigations into aural endolymph and perilymph.

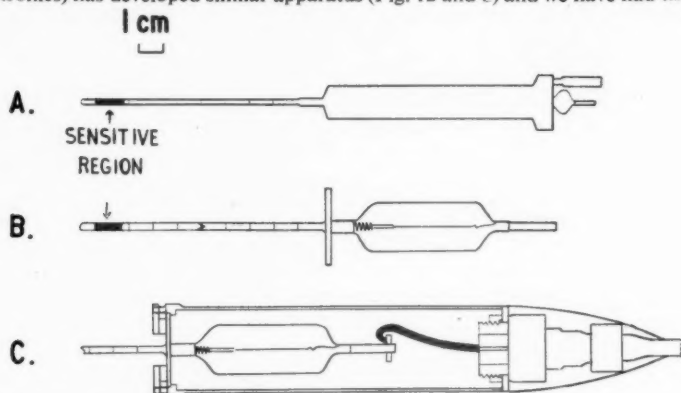
Methods of investigation.—It may be helpful to describe the chief methods available for the study of the radioactive content of tissues.

Let us imagine first that biopsy specimens are available and reasonable counting facilities. The specimen of tissue may perhaps be digested in KOH and the resulting liquid placed in a so-called "liquid counter" consisting of a thin-walled Geiger counter surrounded by an outer vessel containing the liquid (Veall and Vetter, 1952). The number of counts per second is recorded in the usual way and by suitable calibration with a solution containing a known amount of the radioactive material, the content of the tissue may be estimated. This avoids the difficult absolute calibration in terms of geometry of counter and solution. This method is still probably the most generally useful and most sensitive.

An interesting alternative has been developed by my colleague, Dr. E. H. Belcher (1951), and consists of a scintillation counter using a liquid scintillation medium surrounding the specimen, now contained in a small glass tube. This method has the advantage of requiring no chemical treatment and is particularly useful, for example, for small samples of blood. The scintillating medium ($\alpha\alpha'$ -terphenyl in xylene, for example) is in optical contact with the photo-cathode of an electron-multiplier. Each beta particle causes a small flash of light in the medium, which releases electrons from the

photo-cathode; these electrons are amplified many millions of times in the multiplier and the resulting electrical pulse still further amplified and counted.

In some important instances it may be possible to insert a detector actually into the tissues of interest. Naturally such instruments have in general to be as small and mobile as possible, as well as easily sterilized and robust if to be used in an operating theatre. These demands have led to the development of "needle counters" of two types, one a Geiger counter and the second a scintillation system. The former is probably at present the most useful and consists of a thin-walled stainless steel probe about 2-3 mm. in diameter leading to a small glass reservoir of gas (ethyl formate and argon) at 3 atmospheres pressure, electrodes being so designed and constructed as to constitute a Geiger counter sensitive over only a length of about 12 mm. In both America and Great Britain (Morley and Jefferson, 1952) such tubes due to Robinson and Selverstone (Robinson, 1950) have been used, and two examples have been available to us (Fig. 1A). Recently a British firm (20th Century Electronics) has developed similar apparatus (Fig. 1B and C) and we have had the opportunity



A, Robinson-Silverstone 2 mm. Probe. B, 20th Century Electronics 3 mm. Probe. C, 3 mm. Probe in Holder. FIG. 1.—American (A) and British (B and C) Geiger needle counters.

of testing and comparing these counters. Details are available to those interested, but generally we may say that the performance of the two instruments seems to differ little, but cost and availability are heavily on the side of the British equipment. The sensitivity is high, being of the order of 0.7 count/sec. per $\mu\text{c}/\text{ml}$. when immersed in a solution of P^{32} and about 3 counts/sec. for K^{40} . To fix orders of magnitude, when about 1 mc. of K^{40} has been administered to a patient the concentration in a cerebral tumour is often of the order of 7 $\mu\text{c}/\text{gm}$. and in normal tissues perhaps 0.8 $\mu\text{c}/\text{gm}$. The counting rates usually correlate reasonably with the liquid counter estimations of tissue specimens. Such needle counters can be used to explore the brain at operation, typically 15-20 counts/sec. in tumour and 2-3 counts/sec. in normal brain being observed.

We have ourselves spent some considerable effort in an attempt to develop scintillation needle counters with some success. A very fine slip of crystal (NaI) is mounted and inserted into a hollow needle which is filled with a "light guide" of lucite (Perspex), the light being thus conveyed to an electron-multiplier. It is, however, very difficult to maintain good optical contact of crystal and Perspex, while the small size of the crystal and low optical efficiency make for very small light pulses with consequent complexity of subsequent electronic equipment. The multiplier must be cooled with liquid nitrogen to obtain maximum sensitivity, and the flexibility of the light guide system is consequently small and the equipment not very suitable to use in the theatre. The sensitivity for beta rays can hardly be higher, and is sometimes lower than that of a Geiger system since the efficiency for either system is often close to 100%. Recently we have developed methods of moulding crystals into Perspex which may improve the situation but, except in the laboratory for fundamental physical investigations, the Geiger system would seem to be best adapted to clinical use.

Both types of needle may be used in other investigations as, for example, the investigation of the uptake of P^{32} in an amputated breast carcinoma, the sensitivity of the scintillation counters made by us being of the order of 0.3 count/sec. per $\mu\text{c}/\text{ml}$.

Clinical investigations.—We may illustrate the use of these techniques by the results of our investigations into the uptake of radioactive materials in normal brain and various types of tumours first of all using radioactive phosphorus P^{32} .

Stapleton, McKissock and Farran in 1952 studied the uptake of P^{32} in normal brain and brain tumours, expressing the activity in terms of the average specific activity of the whole body, using a liquid counter method. Normal cerebral tissue in the adult has less than half (mean 27%) the average specific activity of the body, while normal adult cerebellar tissue tends to have even lower

values
in only
tumour
from 2
et al.,
the tu
It is
the sub
is requi
cannot
use of
Rece

Fig. 2.—

1.5 MeV
of K are
clusions
external

The 20
period 14
from the
Though
limits of
situ agree

Extern
the so-cal
to the ph
intact sk
We must
soft tissu

values (mean 15%). Satisfactory specimens of both tumour and normal brain tissue were obtained in only 13 of 34 patients and in 12 of these the radioactive phosphorus was concentrated in the tumours in greater amount than in normal brain tissue, values of the ratio of concentrations varying from 2 to 34 : 1. For details of correlation of pathology and uptake the original paper (Stapleton, *et al.*, 1952) must be consulted. There is probably considerable variation in specific activity within the tumour itself.

It is of interest that the concentration of P^{32} , though easily detectable, is not such as to enable the substance to be used therapeutically. For such purposes a concentration of the order of hundreds is required. Unfortunately, too, owing to the low penetration of the beta rays, the concentration cannot be detected outside the intact skull though perhaps further study of the possibilities of the use of the high energy X-rays emitted might be profitable.

Recent investigations making use of K^{42} (emitting 3.6 MeV and 2.1 MeV beta rays and some

SCINTILLATION COUNTER

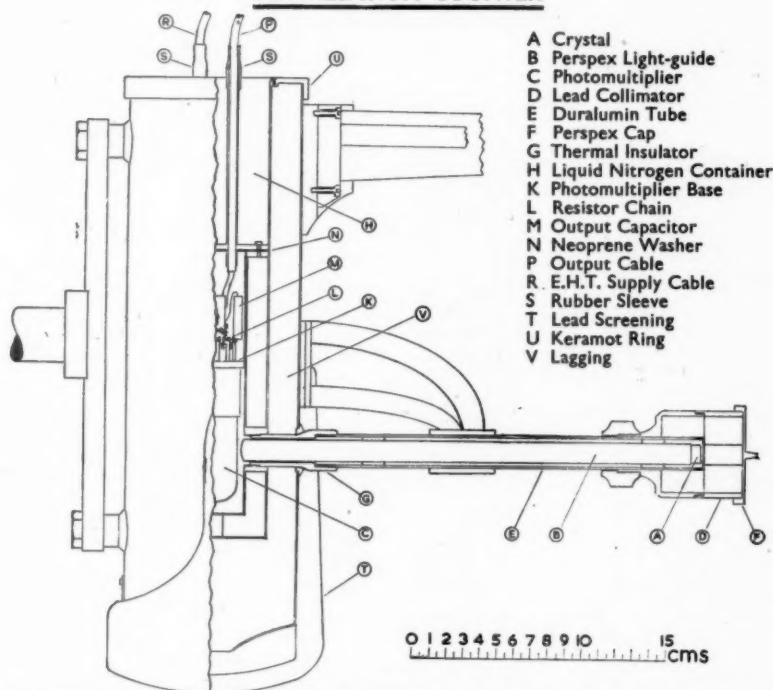


Fig. 2.—Diagram of head unit of scintillation counter. (Reproduced by courtesy of the *Journal of Scientific Instruments*, the *British Journal of Radiology*, and the *British Medical Bulletin*.)

1.5 MeV gamma rays) have given encouraging results. Unfortunately the time-relationships of uptake of K are complex and much more detailed analysis and work will be necessary before definite conclusions can be arrived at, but the results are important as indicating the possibility of the use of external counting methods of detection.

The 20th Century Electronics needle counter has been used in the brains of 15 patients in the period 14.8.52 to 9.12.52. On one occasion the needle was bent through 20° at a point some 5 cm. from the tip but was successfully straightened.

Though the high energy of the beta rays from K^{42} (range 1 cm.) makes the determination of the limits of a tumour inaccurate, when comparison has been possible the ratios of uptake determined *in situ* agree reasonably with those determined from tissue specimens.

External counting.—The other important technique for the study of the radioactivity of tissues is the so-called "external counting". The problems are now quite different but perhaps more fascinating to the physicist. There is no need to emphasize the importance of localization of a tumour in an intact skull and it is therefore easily realized that such a technique is worthy of careful study. We must now use a gamma-ray emitter since the rays must pass to the outside through considerable soft tissue and bone.

Much work has been done with Geiger counters placed near to the body containing radioactive materials, and attempts made to deduce therefrom the distribution of radioactive material in the body. From theoretical consideration of the problem I have, however, come to the conclusion that it is much more difficult than usually realized to deduce the distribution of radioactive isotopes and have therefore attempted to design and construct equipment with high resolving power and precision.

Here the scintillation system comes into its own, for the efficiency of gamma-ray detection by a Geiger system is often only of the order of 1%, and a gain of some 10-50 times may be obtained with the scintillation system under at least as good geometrical conditions. This gain makes possible reasonable times of counting to obtain statistically significant results. The small compact nature of the detector is of great service when we have to design detectors with highly directional properties in small volumes.

We may first describe equipment on these lines used by us in an attempt to use radioactive iodine in diiodofluorescein as a tracer for brain tumours (Belcher and Evans, 1951a, b; de Winter, 1951). The crystal of NaI is situated at the end of a light guide of Perspex which, again, conveys the light flashes to the multiplier (Fig. 2). One of the main experimental difficulties is the fact that the multiplier itself gives a large number of "counts" owing to electronic emission from the photo-cathode and it was necessary for the highest sensitivity to cool the multiplier in liquid nitrogen. The method of cooling may be seen in Fig. 2. The equipment is fitted with an arm and pointer which may be adjusted to a plaster skull cap worn by the patient (Fig. 3) so that the positioning may be

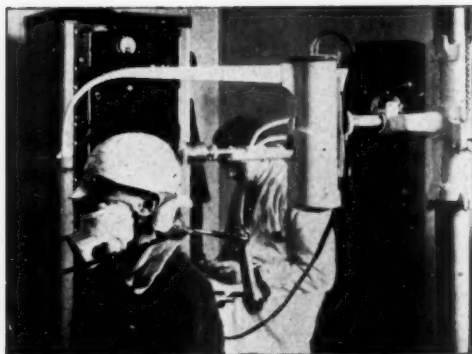


FIG. 3.—Method of examination of patient. (Reproduced by courtesy of the *British Journal of Radiology* and the *British Medical Bulletin*.)

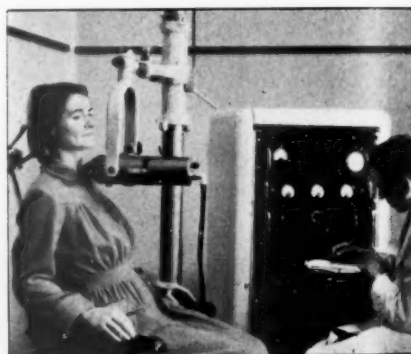


FIG. 4.—Scintillation counting equipment due to Messrs. E. K. Cole Ltd.

very exact, the problem being the inverse of that met in radiation therapy of accurately directing a beam of radiation. By suitable lead stops the crystal may be allowed to "see" varying volumes or alternatively the resolution studied experimentally under known conditions. We have studied both theoretically and experimentally the behaviour of the equipment using as a "phantom" a skull containing a gelatine solution whose activity (0.033 $\mu\text{C}/\text{ml.}$) corresponded to the order observed in the normal brain, experimental "tumours" of varying size, position and radioactive content being inserted for study. In this way the limits of detection may be defined and measured, as shown in the work of my colleagues (Belcher and Evans, 1951a, b).

It was shown to be possible to detect lesions concentrating I^{131} provided that the concentration of activity in the brain was ten times that of the normal brain, and the size of lesion was greater than a certain minimum, depending on the depth. If the depth is 5 cm. the limiting volume was 14 ml., at the centre of the brain 36 ml. These results arise from careful geometrical and statistical studies. A Geiger counter gives such low counting rates as to require prohibitively long examinations to obtain statistically significant numbers of counts.

Recently equipment has been put on the market which, using improved E.M.I. multipliers and a crystal close to the photo-cathode and so used at much better optical efficiency, does not require cooling and with this equipment we have carried out other similar studies (Fig. 4).

Again, we have carried this type of equipment a stage further (Mayneord and Newbery, 1952) in the development of a system which employs a highly directional detector scanning repetitively the tissue of interest (Fig. 5). Each scintillation is recorded photographically and an image of the projection of the radioactive distribution thus built up. Good images of radioactive thyroids have been obtained (Mayneord and Newbery, 1952) and Fig. 6 shows an example of a "tele-autograph" of a model thyroid superimposed on a pinhole picture of a model patient; the equipment is now being extensively redesigned and improved. It is hoped to produce, in addition, a good visual image of a radioactive distribution as well as photographic ones.

Alth
weapo
Use
investi
the use
first se
count
of the
of resu
In o
of cere
much g
20 μC
particu

FIG.
(Repr
of Rad

difficulty
located,
the dete
used emi
The dete
and we a
more sat
The co
the time
with new
In all,
which m
directly,
well arise
Act now
colleagu
investiga
have been

Although the equipment has not yet been used in brain work it seems that it may prove a valuable weapon in this field too, though the difficulties are great.

Use of radioactive diiodofluorescein.—We may conclude with a very short note on two sets of investigations in an attempt to repeat the work of Moore *et al.* (1950) and LeRoy *et al.* (1951) in the use of diiodofluorescein containing I^{131} in the localization of brain tumours. Results of the first series have been published by Belcher, Evans and de Winter (1952). Briefly, with the scintillation counter system described, measurements were made on 34 patients taking great care in the application of the detector, statistical analysis of the results, and development of suitable methods of display of results.

In our hands the method has so far failed to give any definite information as to size and position of cerebral tumours in the great majority of cases investigated. The effect of vascular activity seems much greater than of the activity absorbed in the tissues. Four hours after a dose of 1 mc. only 20 μ c. (2%) can be observed in the brain. This makes the influence of the rest of the body and particularly activity in the liver, of great importance. Here, indeed, we meet the main experimental

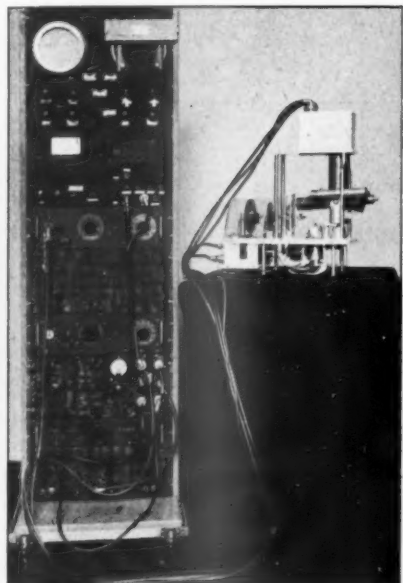


FIG. 5.—Scintillation scanning equipment. (Reproduced by courtesy of the *British Journal of Radiology*.)



FIG. 6.—“Tele-autograph” of model thyroid. (Reproduced by courtesy of the *British Journal of Radiology*.)

difficulty in this external counting method. If the position of a radioactive mass is to be accurately located, a detector “seeing” only through a small aperture is required. Moreover, at a given moment the detector “sees” only a very small fraction of the total activity of the body and if the substance used emits penetrating gamma rays it is very difficult to shield satisfactorily from this stray radiation. The detection of a small increase in concentration in a given area is then fraught with great difficulty and we are at the moment setting up an “observation post” in which we hope to solve this problem more satisfactorily but it means heavy equipment and elaborate layout.

The counter due to Messrs. E. K. Cole has been used on 8 patients having K^{43} and studies made of the time variation of activity in liver, muscle, &c., and over the skull. This work will be continued with new equipment in the near future.

In all, we have developed and are developing a series of physical techniques of interest in neurology, which may well contribute in the future to notable advances in that science; and this, not merely directly, but through the new experimental physiology, biochemistry and pathology which may well arise.

Acknowledgments.—It is a pleasure to acknowledge the helpful collaboration of my medical colleagues, particularly Mr. Wylie McKissock and Professor D. W. Smithers, whose patients were investigated by these methods. I am also indebted to a number of members of my Department who have been responsible for the detailed development of the techniques described.

Finally, my thanks are due to the Medical Research Council and to the Nuffield Foundation for supporting these investigations.

REFERENCES

- BELCHER, E. H. (1951) *Nature*, **167**, 314.
 —, and EVANS, H. D. (1951a) *J. sci. Instrum.*, **28**, 71.
 —, — (1951b) *Brit. J. Radiol.*, **24**, 272.
 —, —, and DE WINTER, J. G. (1952) *Brit. med. Bull.*, **8**, 172.
 DE WINTER, J. G. (1951) *Brit. J. Radiol.*, **24**, 280.
 LE ROY, G. V., TWEEDY, W. R., and ASHKENAZY, M. (1951) *J. lab. clin. Med.*, **37**, 122.
 MAYNEORD, W. V., and NEWBURY, S. P. (1952) *Brit. J. Radiol.*, **25**, 589.
 MOORE, G. E., KOHL, D. A., MARVIN, J. F., WANG, J. C., and CAUDELL, C. M. (1950) *Radiology*, **55**, 344.
 MORLEY, T. P., and JEFFERSON, G. (1952) *Brit. med. J.*, **ii**, 575.
 ROBINSON, C. V. (1950) *Rev. sci. Instrum.*, **21**, 82.
 STAPLETON, J. E., MCKISSOCK, W., and FARRAN, H. E. A. (1952) *Brit. J. Radiol.*, **25**, 69.
 VEALL, N., and VETTER, H. (1952) *Brit. J. Radiol.*, **25**, 85.

Dr. R. D. Keynes: *Some experiments with radioactive isotopes on nervous conduction.*—Most of our knowledge about the mechanism by which peripheral nerve fibres conduct impulses has been derived from studies of their electrical behaviour. This is the most obvious method of approach, and also the only one whose time-resolving power is good enough to analyse the events in different phases of a single nerve impulse. However, it has recently become clear that the electrical changes in an active nerve are intimately connected with a sequence of ionic movements. The "sodium hypothesis" put forward by Professor Hodgkin and his collaborators (Hodgkin, 1950, 1951) postulates that the rising phase of the action potential—its front edge—is caused by an inward surge of current carried by positively charged sodium ions, while the falling phase which follows it is due to an outward current of potassium ions. The work I wish to describe was undertaken because it was obviously essential to obtain direct confirmation—by chemical methods as opposed to electrical ones—of the existence of these ionic movements, and to measure their absolute size as accurately as possible.

Until the advent of flame photometry in the last two or three years, there has been no really simple method of analysing the sodium and potassium contents of tissues and body fluids. The smallest quantity of either which can easily be determined by conventional techniques is about 10 microgrammes. Since the total sodium content of a single nerve fibre may be less than 1 microgramme, even if it is a giant cephalopod axon, ordinary chemical procedures are not very helpful. Fortunately, both sodium and potassium have very convenient radioisotopes, which emit large amounts of strong and easily detected radiation, and these isotopes provide an ideal means for investigating ionic movements. Using Na^{24} there is no difficulty in measuring quantities of sodium well under one-thousandth of a microgramme.

All our work has been done with single giant axons—either those 0.5 mm. in diameter from the mantle of a squid, or 0.2 mm. axons from *Sepia*, the cuttlefish. Using isolated axons restricts the amount of experimental work that can be done, because the animals can only be obtained at certain times of the year, and because experiments are only possible for one or two days after delivery of the short-lived isotopes, while the specific activity is still high. But only by using such axons can reliable absolute measurements be made, giving answers in terms of moles of Na or K moving across unit area of nerve membrane in unit time, and the results have to be in this form if they are to be correlated usefully with the electrical properties of the membrane.

The procedure for observing the movements of radioactive ions is as follows: axons are immersed for a few minutes in artificial sea water made up with Na^{24} or K^{42} instead of inactive Na or K, and are then transferred to a thin-bottomed measuring chamber through which inactive sea water flows, and beneath which a Geiger tube is mounted. A series of counts are taken over several successive ten-minute intervals, followed by another immersion in the radioactive solution, and then a further series of counts. From the amount of Na^{24} or K^{42} found to enter the axon during the short periods in the radioactive medium the inward "flux" of sodium or potassium ions can be calculated (in moles/cm.²/sec.). The outward ionic fluxes are worked out from the rate at which the radioactivity of the axon decreases during the relatively long periods in inactive sea water. The axon can also be stimulated (generally at a frequency of 50/sec.) in both solutions, giving figures for the increases in ionic flux resulting from the passage of impulses. Experiments of this sort have shown (Keynes, 1951) that in an active nerve there is a marked increase in outward potassium flux and in inward sodium flux, as the sodium hypothesis would predict. They have also shown that there is an appreciable turnover of sodium during activity, this again being consistent with the view that the sodium permeability of the nerve membrane is much higher than usual during the rising phase of the action potential.

In order to be able to work out the absolute sizes of the outward ionic fluxes, and to obtain reliable data for the net ionic movements during activity (as opposed to the turnover just mentioned), it is vital to know the total sodium and potassium contents of the axons. This was a stumbling block for some time, because no conventional method of microanalysis is nearly sensitive enough. Dr. Lewis and I eventually overcame the difficulty by using radioisotopes in a rather different way—

applying the technique known as "radioactivation analysis" (Keynes and Lewis, 1951). The principle is very simple. If a small piece of nerve—or any other biological tissue—is put in the big neutron pile at Harwell for a week, all the elements in it become more or less radioactive. It so happens that the Na and K become much more radioactive than anything else likely to be present, so that if the sample is then removed from the pile, and its radioactivity is compared with that of standard samples of Na_2CO_3 and K_2CO_3 which have been irradiated in the same can at the same time, its total contents of Na and K can easily be calculated. This can be done without chemical separation of the Na^{24} and K^{42} in the sample, for while Na^{24} gives very penetrating γ -radiation, K^{42} gives exceptionally strong β -particles, and their separate contributions can be worked out from counts taken with suitable filters, one very thick and the other fairly thin. A correction needs to be made for radiation given by traces of other radioisotopes (chiefly P^{32}), but it is generally less than 2%.

This technique provides a method of microanalysis which is easy to use—as long as there is a neutron pile close by—and far more sensitive than any other. We first applied it to determine the net gain of sodium and net loss of potassium in a series of axons which had been heavily stimulated, and have subsequently used it for routine analyses of almost all the axons used in our tracer experiments.

Our present picture of the mechanism of a nerve impulse is thus that stimulation of the membrane, arising either from the application of a cathode or from activity in a neighbouring region of the nerve, causes a sudden increase in its permeability to sodium ions. Sodium rushes in, because the external concentration is much higher than the internal one, and this inflow of current shifts the membrane potential from its resting level to a new value where it is reversed by about 50 mV. Next the membrane loses its high sodium permeability, and becomes instead very permeable to K^+ ions. The potassium concentration is highest inside, so there follows an outflow of current carried by potassium ions, bringing the membrane potential back to its original level. The impulse has passed, leaving the nerve with slightly more Na and less K than it had before. The tracer evidence I have just described agrees very well, both qualitatively and quantitatively, with this explanation of the events during nervous activity. So far, our work has been concerned wholly with non-myelinated invertebrate nerves, but recent studies of conduction in myelinated vertebrate nerves (Huxley and Stämpfli, 1949, 1951) suggest that there the sequence of events is similar, except that the active changes in membrane potential are restricted to the nodes of Ranvier.

Obviously the story is still far from complete. In the living animal the sodium and potassium contents of the nerve fibres do not normally vary much, so that some recovery process must exist to extrude sodium and absorb potassium. This process will need energy to drive it, since both ions are being moved against their concentration gradients—from weak to stronger solutions—and it is here that the metabolism of the nerve becomes important. The recovery mechanism only needs to be able to deal with the average ionic interchange over relatively long periods, since the initial high K and low Na of the nerve provides an energy reserve which allows the conduction of short bursts of impulses without any re-charging. The problem as to exactly how the recovery mechanism works, and as to how metabolism is linked to it, is an extremely interesting one, and tracer methods are likely to prove an effective tool for investigating it. Professor Hodgkin and I have recently made a start at this work, and have found that certain metabolic poisons will reversibly reduce the rate of sodium extrusion by axons recovering from stimulation, to a very low value, without any marked effect on their excitability (Hodgkin and Keynes, 1953). This is perhaps the point at which my remarks come closest to being of direct medical interest, but it will probably be some time before any clear picture of recovery emerges.

REFERENCES

- HODGKIN, A. L. (1950) *Brit. med. Bull.*, **6**, 322–325.
 — (1951) *Biol. Rev.*, **26**, 339–409.
 —, and KEYNES, R. D. (1953) *J. Physiol. Proceedings*, March.
 HUXLEY, A. F., and STÄMPFLI, R. (1949) *J. Physiol.*, **108**, 315–339.
 — (1951) *J. Physiol.*, **112**, 496–508.
 KEYNES, R. D. (1951) *J. Physiol.*, **114**, 119–150.
 —, and LEWIS, P. R. (1951) *J. Physiol.*, **114**, 151–182.

Mr. T. P. Morley: This report is based on the experience gained at the Manchester Royal Infirmary from the use of P^{32} in 53 neurosurgical cases.

As Professor Mayneord has indicated the early promise of localization of brain tumours using the detection of labelled isotopes by external, non-surgical measures, has only partly been fulfilled. The criteria of success of any such method must be (i) the replacement of established aids to diagnosis (ventriculography, arteriography), or (ii) the addition of information about the situation of a tumour which those other methods fail to provide. So far the methods of external localization that have been developed have not satisfied these criteria. 65% success in localization has been claimed in a recent report (Peyton *et al.*, 1952), but the authors allow a "corrected" percentage of 94 when clinical data are combined with the findings of the scintillator detector. Most neurosurgeons will be sceptical of the adjusted figure and judge the method by the number of times localization was obtained unaided by clinical considerations—i.e. 65%. At the same time it is acknowledged that any such aid can only be used in support of clinical examination. Accurate localization will have to be obtained in a far

higher proportion of cases (nearing 100%) before the method will replace others, such as arteriography and ventriculography, where the inherent danger is outweighed by the high proportion of accurate localizations.

The principle of the use of phosphorus in the detection of brain tumours is that there is a high concentration of phosphorus in a cellular tumour in comparison with the relatively sparse cell population of the surrounding brain. If a tracer dose of radioactive phosphorus is injected intravenously it is distributed throughout the tumour as it is throughout the rest of the body wherever phosphorus normally resides. The tumour may then be located by inserting into it a Geiger-Muller probe counter the same size and shape as an orthodox brain cannula. Since the beta particles given off by the phosphorus atom travel only 5 mm. through brain tissue the sensitive tip of the probe must be inserted to within that distance from the tumour before a high rate of count, and hence detection, is obtained. Thus the situation of the tumour can be determined with a considerable degree of precision.

The equipment required has been listed and illustrated in a previous report (Morley and Jefferson, 1952). It is cheap, simple to use, portable, and the all-metal probe is easy to sterilize and reasonably robust. One type of probe put on the market has a glass gas chamber, an external diameter of 3 mm. rather than 2 mm., and requires a modified technique for sterilization, all of which are practical disadvantages. The method may be applied in the following ways. (a) In securing needle biopsy specimens through a burr hole. Of 22 such procedures undertaken, 20 were successful in that positive biopsy specimens were obtained, and of the remaining 2, in one autopsy proved that no tumour was present, and in the other the probe had not been passed in the right direction; the tumour had been missed by a centimetre. This number of positive biopsy specimens was considerably higher than had been obtained before the use of the Geiger probe. (b) In planning the incision in the brain where the tumour lies deep and invisible. (c) In mapping the extent of a tumour and discovering its operability. On occasions it can give useful information regarding the presence of tumour left behind after excision has been performed.

The test is not specific for any type of tumour and the pathological variety cannot be deduced from the rate of counts, as the following table demonstrates:

	Cases	Average counts
Meningioma	8	25
Secondary carcinoma	8	25
Glioblastoma	14	21
Astrocytoma	12	7

An enhanced count rate is found also in granuloma, and in the periphery of an abscess and, to a lesser extent, in recent infarcts—in fact in any condition, neoplastic or inflammatory, in which the density of cell nuclei is greater than in the surrounding brain. It is this that decides whether or not the phosphorus is concentrated in any area, and it is not necessary to postulate a breakdown of the several membranes that lie between the circulating blood and the cell nucleus—the so-called blood-brain-barrier. While it has been shown (Hardman, 1940) by histological methods that the endothelium of capillaries and sinusoids in malignant brain tumours lacks continuity, the same cannot be demonstrated in granulomas or slow-growing meningiomas, both of which concentrate the phosphorus well in comparison with surrounding brain by virtue of the greater cell density.

REFERENCES

- HARDMAN, J. (1940) *Brain*, 63, 91.
 MORLEY, T. P., and JEFFERSON, G. (1952) *Brit. med. J.*, ii, 575.
 PEYTON, W. T., MOORE, G. E., FRENCH, L. A., and SHELLEY, N. C. (1952) *J. Neurosurg.*, 9, 432.

Mr. M. A. Falconer: said that he thought that in a case cited by Mr. Morley a needle-biopsy of the tumour could have been obtained without resort to isotope methods of localization. A tumour circulation, probably gliomatous, was clearly shown in the lateral arteriogram. The position of the tumour with regard to the sagittal and coronal planes was thus known, and only its depth from the lateral surface remained to be determined. An antero-posterior radiograph would probably have given this information. However, if such a view were unobtainable, the tumour could still have been located by making a burr hole on the lateral aspect of the skull directly over the tumour, and passing a brain-needle inwards to varying depths, while simultaneously moderate suction from a rubber bulb was applied to the needle. If the tumour were firm, resistance would be encountered when it was reached, and the suction could then be increased so as to draw up a pledget of tumour. If the tumour were soft, no resistance would be felt, but, with the lighter degree of suction, soft tumour tissue was more likely to be drawn up into the needle than the firmer surrounding brain substance. In his experience one was able in this way to obtain biopsy material in nearly all cases of malignant supratentorial glioma, as well as in many of the more differentiated tumours.

Mr. Morley, in reply to Mr. Murray Falconer, said that if he had had such great success with taking needle biopsies through a burr hole, then he had no need for this method. But it had been Mr. Morley's experience, and the experience of many other neuro-surgeons and neuro-pathologists, that the number of positive biopsies obtained by blind needling was distressingly low.

If w
iodine
in the
in bon
reactin
Even
and or
of exp
in thei

To-
clini-
will be
in thei
This,
applica
thyroid
say, io
fact, th
of elec
iodine
atoms,
and an

We
telluriu
will be
iodine.
mata,
cause I

Loca
counte
between
the vic
and a
recorde

Loca
surrou
at whic
of such
deep w
penetra

(Dr.
This
ing wh
also, si
the cou
ing a p

Section of Surgery

President—Professor F. A. R. STAMMERS, C.B.E., T.D., Ch.M., F.R.C.S.

[December 3, 1952]

DISCUSSION ON THE USE OF RADIOISOTOPES IN SURGERY

Dr. E. E. Pochin, Director, Department of Clinical Research, University College Hospital Medical School, London.

The Investigation and Therapy of Thyroid Carcinoma with Radioactive Iodine¹

If we had been meeting ten years ago to discuss this subject, we should have heard that radioactive iodine was concentrated in the human thyroid, that radiophosphorus was taken up by lymphoma tissue in the mouse, that radioiron entered the red cells of the dog, and that radiostrontium was concentrated in bone in the rat. We might, or might not, have been told that the first plutonium pile had been reacting for two days.

Even five years ago, when reports were appearing on radioiodine and radiophosphorus therapy, and on radiosodium and radioiron in diagnosis, our discussion would have been of a widening field of experimental methods—methods of the greatest interest and promise, but still tentative and uncertain in their clinical importance.

To-day, I think the position is changed. The radioactive isotopes now offer methods of proved clinical value, and we are now participants rather than spectators, in the sense that certain of our patients will be inadequately treated or examined if we do not make appropriate use of isotope methods. This, therefore, appears to be an appropriate stage to review some of the most important clinical applications of these techniques. As one example, I wish to discuss the investigation and therapy of thyroid carcinoma with radioactive iodine. To start by a definition of terms, a radioactive isotope of say, iodine, is merely a variant form of iodine which happens to be radioactive. Its atoms have, in fact, the same electrical charge in their nucleus as for ordinary iodine, and hence the same number of electrons surrounding the nucleus, and therefore identical chemical properties; so that, wherever iodine is concentrated, radioiodine will be equally concentrated and with the same speed. But these atoms, although having the same charge as ordinary iodine, are abnormal in their atomic weight, and are consequently unstable, and undergo radioactive disintegration.

We may therefore take radioactive iodine, which Harwell produces by neutron irradiation of tellurium, and administer it, in a simple chemical solution in the form of iodide, and know that it will become distributed through the body in the same way and at the same speed as for ordinary iodine. But in the areas where it is concentrated, namely in the thyroid and in some thyroid carcinomata, it will reveal its presence by the radiations that it emits or, if very high doses are used, will cause local tissue destruction by the intense radiation produced.

Local concentrations of, for example, radioiodine, may be detected by using a suitably shielded Geiger counter. The counter itself consists essentially of two wires in a tube with 1,000 volts potential difference between them, but insulated from each other so that no current flows. But if a radioactive atom in the vicinity breaks down, the radiations from it may momentarily ionize the gas between these wires, and a current will flow. The counting rate, or the frequency with which such currents flow and are recorded, will thus be proportional to the amount of radioactive isotope in the vicinity of the counter.

Localization of a source with such a counter can clearly be made much easier if the counter is surrounded by a cylindrical lead shield, so that it detects only those concentrations of radioisotopes at which the end of the counter is directly pointed. It is then obviously possible to detect the presence of such areas of concentration, to distinguish adjacent areas and to do so even when these areas are deep within the body, using the gamma radiation which is emitted by most radioisotopes and which penetrates tissue freely.

(Dr. Pochin then demonstrated these methods of localization.)

This principle obviously applies, not only to finding where an isotope is concentrated, but to detecting when such material, injected intravenously, arrives at any particular position in the body. Clearly also, since the counting rate is proportional to the amount of isotope present at a given distance from the counter, it can be used to estimate quantitatively the efficiency of an organ or a tissue in concentrating a particular element; as for iodine in the thyroid, iron in the blood, mercurial diuretics in the

¹ Based on work undertaken for the Medical Research Council.

urine, or phosphate in the head of a fractured femur as a measure of its vascularity; and in many other instances.

The application of these methods may be illustrated in the selection of thyroid carcinomata for radioiodine treatment. It is familiar that certain of these tumours resemble normal thyroid tissue in having the capacity to concentrate iodine, although rarely as strongly as does the gland itself. It is obviously important, in any individual case, to find whether the carcinoma does concentrate iodine strongly for, if so, it may respond to treatment from the intense local irradiation produced within the tumour by the radioiodine there concentrated. Moreover, most of this radiotherapeutic effect is achieved by the beta radiation of the radioiodine which only penetrates a millimetre or so from sites of concentration of the isotope, so that very high tumour irradiation may be achieved with only moderate radiation of the body or of neighbouring structures.

The most direct method of detecting uptake of radioiodine in a thyroid carcinoma is by measuring the radioactivity of tumour tissue removed at biopsy a few days after a test dose of radioiodine, or by comparing its activity with that of a plasma sample taken at the same time. When, however, the biopsy material is taken from the neck, and might include some normal thyroid tissue, an autoradiograph will usually be necessary to show that radioiodine is taken up in carcinoma tissue itself.

In most cases, however, repeated measurements will be required during the course of treatment, of the radioiodine uptake of the tumour or of its various metastases, and serial biopsies of carcinomatous tissue are very rarely justifiable. In practice, therefore, the detection of uptake commonly relies on external counting, that is, on mapping the sites of radioiodine concentration throughout the body by the use of a counter external to the body surface. If the problem at this stage were simply one of giving a test dose of radioiodine and testing for its uptake in tumour metastases, the selection of cases suitable for radioiodine treatment would be a technical rather than a clinical problem, and the results would be simple although discouraging since, in fact, such uptake in tumours is rarely detectable while any normal thyroid tissue remains in the body. It has, however, frequently been shown (Rawson *et al.*, 1948; Dobyns and Maloof, 1951; Pochin *et al.*, 1952) that this radioiodine uptake may only develop or become detectable in tumour tissue after ablation of the thyroid, either by a total thyroidectomy or after thyroid destruction by radioiodine. Of these two alternatives, the surgical removal of all thyroid tissue is the preferable, as avoiding unnecessary radiation dosage and allowing radioiodine treatment to be started several weeks earlier. Commonly, however, it will be impossible to be sure of removing the entire thyroid from an area in which previous biopsies or thyroidectomies have been performed and which is involved with carcinomatous tissue. In such cases the thyroid can be destroyed by a first therapeutic dose of radioiodine.

The decision to ablate the thyroid by either process must usually be made, therefore, without knowledge whether the tumour is capable of concentrating radioiodine, and such thyroid ablation should clearly be limited to those patients in whom the tumour is likely to develop or reveal powers of iodine concentration as a result of it. It has been found that anaplastic thyroid carcinomata rarely show such powers even after thyroid ablation, whereas the more differentiated ones appear to do so rather frequently. This may be illustrated from the results observed in a short series of such tumours and shown in Table I, from which it will be seen that radioiodine concentration was probably occurring

TABLE I.—RADIOIODINE UPTAKE DEMONSTRABLE IN THYROID CARCINOMATA

	(Cases)	Radioiodine uptake	
		Certain	Certain or probable
Of all tumours	(35)	26%	46%
Of all differentiated tumours	(21)	43%	62%
Of all differentiated tumours after thyroid ablation	(16)	50%	75%

in three-quarters of the differentiated tumours examined after thyroid ablation, although in less than half of the whole series, being infrequently seen unless the tumour structure included well-formed alveoli, or follicles containing colloid secretion.

It appears, therefore, that all thyroid carcinomata which cannot be removed radically by operation should, if possible, be examined by biopsy. Those which are found on biopsy to possess a well-differentiated histological structure, particularly if colloid is present, should be subjected to thyroid ablation by the total removal of normal thyroid tissue at operation if this seems likely to be practicable, or otherwise by radioiodine. The tumour should then be tested for its capacities of radioiodine concentration, although evidence of such uptake may possibly have been indicated during a radioiodine ablation by tenderness or reduction in size of tumour metastases, as well as of normal thyroid tissue, during the week after the "ablation dose". If radioiodine concentration can be demonstrated in the tumour tissue, successive therapeutic doses of radioiodine are given at intervals of two to four months until no further abnormal sites of radioiodine concentration can be detected in the body. Myxoedema will have developed in such cases after the thyroid ablation and can be controlled by thyroxine except during the weeks immediately preceding each successive therapeutic dose, of which the uptake in tumour tissue would be inhibited by current or recent thyroxine therapy.

This should that it cases is be mai valua sized re

DOBY
POCH
RAW
End

Dr. F.

I sha shall be and is p isotonic half-life small; without

Amor namely injected of Sodi of the b

The fi on the s in a case and the

FIG

This form of therapy has not been continued sufficiently long to indicate its scope, or whether it should be regarded as a palliative or as a possibly curative treatment. It does appear already, however, that it is valuable in the majority of all histologically differentiated thyroid carcinomata, and in such cases is commonly associated with relief of symptoms or reduction of tumour mass which can often be maintained, at least for several years. This form of treatment is distinctive, also, in that it is often valuable and may prove curative, even though it is only started when the tumour has already metastasized remotely in bone, lungs, or through lymphatic channels.

REFERENCES

- DOBYSN, B. M., and MALOOF, F. (1951) *J. clin. Endocrin.*, **11**, 1323.
 POCHIN, E. E., MYANT, N. B., HILTON, G., HONOUR, A. J., and CORBETT, B. D. (1952) *Brit. med. J.*, **ii**, 1115.
 RAWSON, R. W., MARINELLI, L. D., SKANSE, B. N., TRUNNELL, J., and FLUHARTY, R. G. (1948) *J. clin. Endocrin.*, **8**, 826.

Dr. F. T. Farmer, Physicist, Royal Victoria Infirmary, Newcastle upon Tyne:

Application of Radioisotopes as Tracers in Surgery

I shall deal in this paper with some of the applications of radioisotopes as tracers in surgery, and shall be concerned primarily with the use of Sodium²⁴. This substance has a half-life of fifteen hours, and is particularly suitable for tracing movements of body fluids, since when made up in the form of isotonic NaCl solution, it is completely miscible with the blood or extra-cellular fluid, and its short half-life means that it is only active in the body for a limited time and the risk of radiation injury is small; at the same time the penetrating gamma rays emitted enable measurements to be made from without the body and therefore with little disturbance to the patient.

Among a great number of applications of this isotope, two main classes have been of particular use, namely the measurement of blood velocity by observing the time of transit of a small quantity of injected radiosodium from one point to another in a vein or artery, and the study of "clearance rates" of Sodium²⁴ when injected into the tissues and allowed to be carried away by the dispersive processes of the body.

The first class of test requires an injection of between 2 and 10 $\mu\text{c.}$, and a detector of radiation placed on the skin at a suitable distance from the site of injection, and Fig. 1 shows the result of such tests in a case of peripheral vascular disease. The sodium was injected into the saphenous vein at the ankle and the two curves show the radiation intensity picked up at the groin as a function of time, firstly

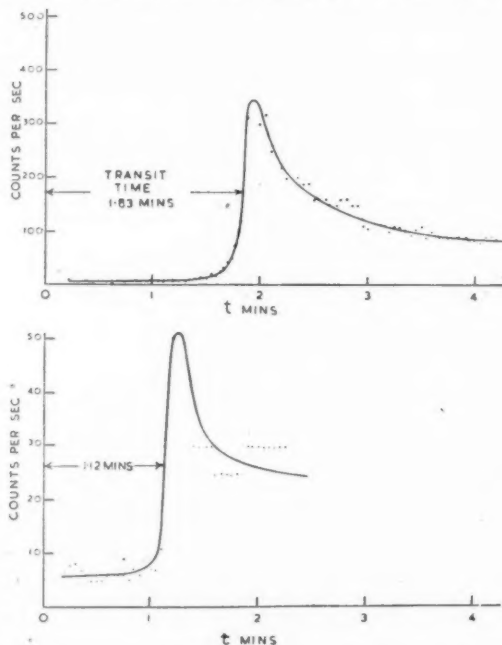


FIG. 1.—Circulation time measurements from ankle to groin; injection of Na²⁴ into saphenous vein.

with the patient at rest and secondly when the limb was exercised. The time in either case is much longer than that for a healthy limb and the extent to which the flow is speeded up by exercise is readily seen. (In the second experiment only about one-fifth of the quantity of sodium was used, resulting in a higher background "count" and correspondingly reduced accuracy of measurement.) Much detailed work of this nature has been carried out, particularly by Osborn and Payling Wright (1949) and by Payling Wright (1952), using an automatic recording arrangement designed to assist the accurate measurement of these circulation times. In this, a record is drawn on a kymograph drum, each point representing the total number of counts picked up by the detector since the start of the experiment. The slope of the graph thus indicates the counting rate or intensity of radiation, and the moment at which the sodium arrives at the counter is shown by sudden change in slope. These authors have applied the method to the study of venous velocity in the leg particularly during pregnancy, making the injection into the foot and recording over the groin, and they found a progressive diminution of velocity, the transit time from foot to groin increasing from about 10 seconds at the commencement of pregnancy to over two minutes at the first stage of labour. This slowing down of blood flow has obvious importance in relation to the danger of thrombosis and may be used as a guide to treatment, and the method has been applied with equal effect in the study of circulation times under other abnormal conditions.

The use of Sodium²⁴ for measurement of "clearance rates" was first introduced by Kety in 1948, who showed that when a small quantity of this substance was injected into the muscle and the amount remaining at any time was measured by the gamma rays reaching a counter over the skin, the dispersal followed an exponential law, diminishing to half in equal successive intervals of time. By making certain simple assumptions, namely that the sodium lies initially in the extra-cellular space of the tissues and is confined to a fixed volume until it is carried away by the blood vessels or lymphatics, he showed that this is the form of clearance curve that would be expected, and suggested that the rate of clearance might be a useful index of the overall exchange fluid within the tissue. It seems from the work of Stone and Miller (1949) and others that lymphatics play a negligible part in the clearance process and that the sodium is carried away almost entirely by penetration into the blood capillaries. It must be remembered that sodium ions are of much lower molecular weight than most physiological substances, but nevertheless there is much evidence that such clearance measurements give a valid indication of the rate at which nutrient fluids are being supplied to any point and that at which metabolites are carried away. The result may bear very little relation to the rate of blood flow, as has been demonstrated by Miller and Wilson (1951), but on the other hand is likely to be a more valuable index of physiological function of the tissues than is a simple measurement of this rate of flow.

This technique has recently been applied to the study of skin grafts in plastic surgery. For this purpose an injection of about 0.1 c.c. of isotonic saline containing 1 μ c. or so of Na²⁴ is made intradermally and a counter is placed over the wheal so formed; a special counter tube¹ has been designed for such measurements having a thin end window of glass which allows, if desired, the beta rays as well as the gamma to enter and so give the maximum sensitivity of detection. It is necessary to mount the counter on a light freely moving support, and locate it by some simple attachment to the part of the body concerned, so that its position in relation to the skin remains accurately constant despite breathing and other movements of the patient. No lead screening is needed on the counter. This arises from the fact that a high counting rate is necessary in any case to record the rapidly changing activity, so that the background due to stray radiation contributes a negligible proportion to the reading on the instrument. Fig. 2 shows typical results of such measurements on an intradermal wheal, where the activity is plotted to a linear scale against time. The form of curve is seen to be exponential, and it is convenient to plot the results to a logarithmic scale on the vertical axis, so that a straight line is produced. Fig. 3 shows such results in which the lower curve was obtained with a 1 mm. aluminium filter over the end of the counter, cutting off the beta-rays, and the line is seen to be straight from the start of the experiment. When the filter is removed so that the beta rays enter, there is an initial rise, probably due to diffusion of sodium towards the counter, and this arrangement, though reducing the quantity of sodium needed to about 0.2 μ c., is more susceptible to movement of the counter or patient. In either case the slope of the straight line gives a measure of the rate of loss of sodium, and a simple scale, drawn on a transparent material, yields the clearance rate as a percentage loss per minute.

When such measurements are made on normal skin, large variations in clearance rate are observed which are attributable to the many complicating factors, including temperature, drugs and even mental apprehension of the patient which may exist. The effect of temperature has been studied in a series of experiments on the skin of the hand, and it has been found that at room temperature a rise of only one degree centigrade causes an increase of some 24% in the clearance rate. In any such work therefore on normal skin accurate temperature control is needed, and it is clear that single measurements alone will generally give little information about the condition of the skin at the point in question, and in all such work steps must be taken to eliminate the disturbing factors as far as possible.

Fortunately, when the method is applied to skin grafts these difficulties are minimized, since the skin is to a large extent denervated and is relatively independent of temperature and other disturbing

¹ 20th Century, type MB4H.

influen
the cle
measu
heat e
atropi
applie
thorac
seen th
after t
and af
ments
afford
In ord

COUNTING RATE

FIG. 4.

FIG. 4.

influences. It has been found in consequence that when an injection is made intradermally into a graft the clearance rate forms a significant index of the fluid transfers taking place and thus gives some measure of the viability of the tissues. This method is a more objective test than measurements of heat exchange (Douglas and Bucholtz, 1943) or the use of fluorescein (Lange and Boyd, 1944) or atropine (Hynes, 1948) which have previously been employed to this end. The technique has been applied extensively to tubed pedicles. Fig. 4 shows the clearance rates so obtained in an acromio-thoracic pedicle before, immediately following, and after the raising of the tube in this area. It is seen that before surgical interference the clearance rate in the skin was 5.1% per minute; thirty minutes after the operation, although the pedicle looked clinically very healthy, the rate was practically zero; and after an interval of seven days it had increased to 3.3% per minute. By making such measurements at daily intervals after formation of a pedicle, a valuable guide to its increasing vascularity is afforded, and Barron, Veall and Arnott (1951) have applied this technique on a considerable scale. In order to facilitate measurements, they have introduced a recording system which first converts

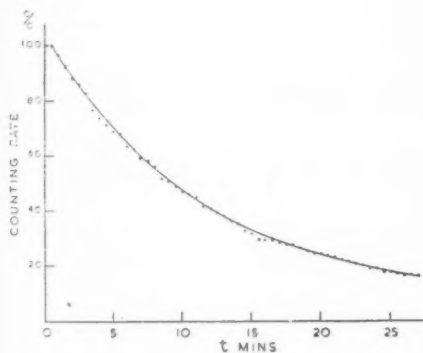


FIG. 2.—Clearance of Na^{24} from intradermal wheal (γ -ray measurements) to linear scale.

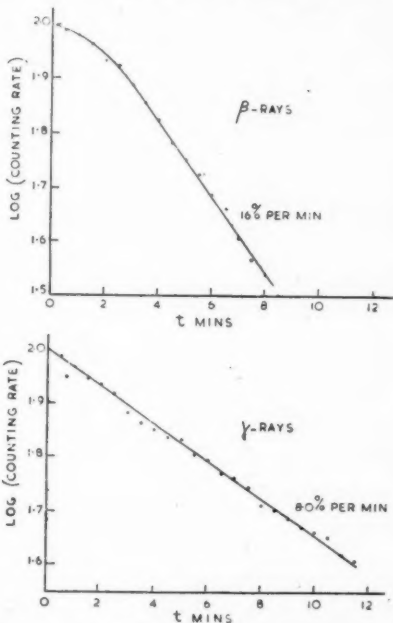


FIG. 3.—Clearance of Na^{24} from intradermal wheal without and with Al filter over counter window.

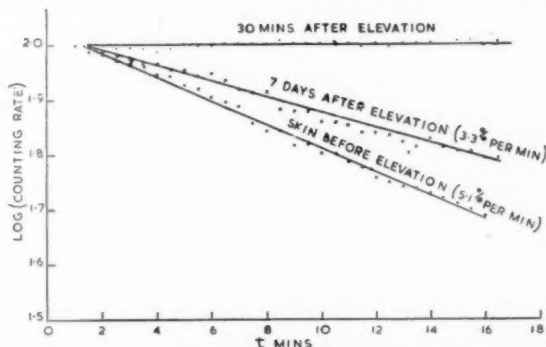


FIG. 4.—Clearance of Na^{24} from intradermal wheal before, immediately following and seven days after raising of pedicle on chest.

the counting rate of a Geiger tube to a logarithmic scale, and then records this on a moving paper, and by making two or three injections successively at different points on the pedicle, increased information can be obtained. Such daily measurements enable the successive stages of an operation to be planned and carried out often very much earlier than would have been the case with no such tests, and in consequence the overall time of a multiple stage graft may be reduced in some cases from several months down to as many weeks.

In the intermediate stages of a pedicle operation, when one or other end of the tube is about to be transferred to a new site, it is important not only to know whether the circulation is proceeding through the pedicle, as shown by the tests described, but also to predict whether there will be an adequate fluid supply to the tissues when the pedicle is divided at one end and the circulation has to take place from the other end through the length of the pedicle and back again. A modified form of radio-sodium test has proved valuable in these cases, in which an injection is made at some convenient point in the tube, and a clamp is applied to one or other end, so obstructing completely the through-circu-

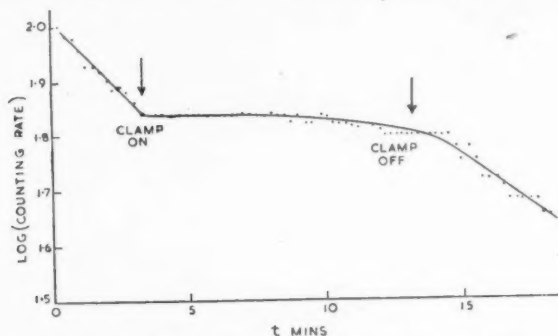


FIG. 5.—Effect of clamping one end of acromio-thoracic pedicle. Clearance of Na^{24} from centre is completely arrested then recovers as new vascular channels open up.

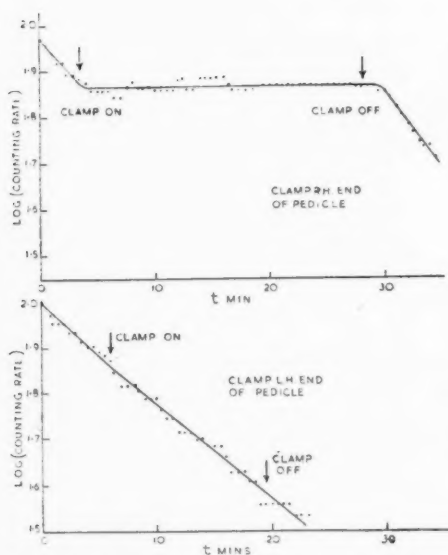


FIG. 6.—Clearance of Na^{24} from pedicle clamped at L.H. and R.H. ends. There is no flow through the L.H. end of the tube.

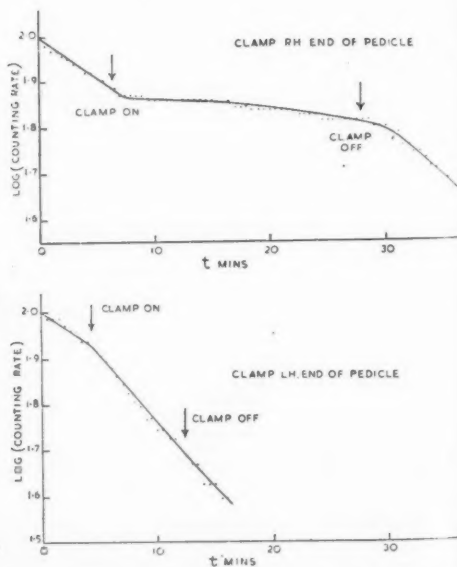


FIG. 7.—Clearance of Na^{24} from the same pedicle after one week showing now some circulation through L.H. end.

lation
end. Fr
necrosis
week.
that the
as show
The m
end was

Further
relatively
it. Mak
and then
and it is
clamp w
Fig. 7 t
less than
hand en
could sa
more us
saving i
operati

The n
hazard.
exceed
avoid e

The a
problem
treatme
full ope

The
known
than in
contain
About
ments o
report
Moore
accurac
goes in
et al. (1
these di
they we
these, a

The
brain t
the ope
country
steel ab
of p₂₂,
length
detection
has the
and a n
and Jeff
where a
a cann
tumour
depths
tumour
agreem
may en
has un
wide)

lation. Any clearance which remains is then due to the forward and back circulation from the other end. Fig. 5 illustrates such a case. This patient had an acromio-thoracic pedicle raised for a radio-necrosis of the mandible, and radio-sodium measurements were made on it at intervals of about a week. In the test shown, a clamp was applied to the right-hand end of the pedicle, and it is seen that the flow came almost to a standstill and then, in the following ten minutes, it gradually increased, as shown by the slope of the graph, indicating that new pathways were opening up in the dermis. The medial end of the pedicle was transferred shortly after this and after four weeks the acromial end was also transferred to the face.

Further tests were made at this stage. It was known that the left-hand end of the pedicle was in a relatively unhealthy condition clinically and it was suspected that there was poor circulation through it. Making an injection at the centre of the pedicle and applying a clamp first to the right-hand end and then on the next day to the left-hand end, the clearance rates as shown in Fig. 6 were determined, and it is apparent that in the first of these the blood supply was stopped almost completely by the clamp while in the second it was hardly affected. A week later the test was repeated and it is seen from Fig. 7 that there was now some circulation from the left-hand end, though this was still very much less than from the right. This process was continued until a clearance rate after clamping at the right-hand end of 2% per minute was obtained, and it was then decided that the final spreading of the pedicle could safely be undertaken. Tests of this type can be used effectively on most pedicle grafts and give more useful information than a simple clearance rate measurement without clamping. Often a great saving in overall time in hospital can be effected by applying this technique at various stages in a graft operation.

The radiation dose given to the patient by these injections is quite small and presents no serious hazard, and even when gamma-rays are used, requiring a greater amount of Sodium²⁴, it does not exceed that received in an ordinary diagnostic X-ray examination. Care must be taken, however, to avoid exceeding a safe level by repeated injections in the same area.

The application of radioisotopes to brain surgery.—Two lines of attack have been made on this problem. The first consists in localization of tumours from without the body as an aid to subsequent treatment, and the other the detection of malignant tissues within the brain, either during biopsy or full operative procedure.

The first technique has been developed from the use of dyes such as sodium fluorescein which were known to concentrate in highly cellular tissues and thus exhibit a higher uptake in a tumour mass than in the surrounding brain medium. Recently a derivative, di-iodofluorescein, has been produced containing Iodine¹³¹, which emits gamma-rays and can thus be detected in very small quantities. About 1 mc. of this substance is given by intravenous injection and one to two hours later measurements of the radiation are made with shielded directional counters around the head. Davis *et al.* (1950) report 200 cases investigated in this way, in 95% of which the tumour was correctly localized, and Moore and his co-workers (1950) also report success with this method. The technique requires high accuracy of measurement and is hampered by the fact that only about 2% of the radioiodine injected goes into the brain, a large proportion going into the thyroid, and recently in this country, Belcher *et al.* (1952) have introduced a scintillation counter designed to give added sensitivity and overcome these difficulties as far as possible. Their results, however, did not confirm the earlier publications and they were able to verify only 20 out of 34 intracranial tumours and to locate satisfactorily only one of these, and as yet the earlier results have not been borne out by them or other workers.

The second technique, namely that of localization in the operating theatre, consists in mapping out brain tumours using a beta-ray emitter, phosphorus³², injected into the body 15–30 minutes before the operation. It was introduced by Selverstone *et al.* (1949) and has been used considerably in this country, notably by Morley and Jefferson (1952). These workers used a probe counter made of stainless steel about 2 mm. diameter and having its sensitive portion near the tip, and gave an injection of 1 mc. of P³²; counting rates in the tumour were then found to range from 2 to 50 times background. The length of path of the beta-rays in the tissues is only about 5 mm., and the method therefore limits the detection to that of radioactive material in the immediate neighbourhood of the counter: this, however, has the advantage that even quite large quantities of the isotope at greater distances cause no effect, and a more accurate localization can be made than with a gamma-ray emitting substance. Morley and Jefferson report successful use of this technique for obtaining biopsy material in 14 out of 15 cases, where an exploration is made at varying depths with the probe and then aspiration carried out along a cannula introduced through a burr hole. They also report successful mapping out of sub-cortical tumours in which the counter is sunk at several places, and at each measurements are made at varying depths to determine the boundary of the tumour. Such measurements often determine whether a tumour is accessible before excision is attempted, and post-mortem examinations have confirmed agreement between the areas so mapped out and the actual extent of the tumour. Misleading results may on occasion be given by inflammatory lesions in the brain which also take up P³², but the method has undoubtedly very great value in the surgery of brain tumours and is likely to be applied more widely in the future.

REFERENCES

- BARRON, J. N., VEALL, N., and ARNOTT, D. G. (1951) *Brit. J. plast. Surg.*, **4**, 16.
 BELCHER, E. H., EVANS, H. D., and DE WINTER, J. G. (1952) *Brit. med. Bull.*, **8**, 172.
 DAVIS, L., MARTIN, J., ASHKENAZY, M., LEROY, G. V., and FIELDS, T. (1950) *J. Amer. med. Ass.*, **144**, 1424.
 DOUGLAS, B., and BUCHOLTZ, R. R. (1943) *Ann. Surg.*, **117**, 692.
 HYNES, W. (1948) *Brit. J. plast. Surg.*, **1**, 159.
 KETY, S. S. (1948) *Amer. J. med. Sci.*, **215**, 352.
 — (1949) *Amer. Heart J.*, **38**, 321.
 LANGE, K., and BOYD, L. J. (1944) *Arch. intern. Med.*, **74**, 175.
 MILLER, H., and WILSON, G. M. (1951) *Brit. Heart J.*, **13**, 227.
 MOORE, G. E., KOHL, D. A., MARVIN, J. F., WANG, J. C., and CAUDILL, C. M. (1950) *Radiology*, **55**, 344.
 MORLEY, T. P., and JEFFERSON, G. (1952) *Brit. med. J.*, **ii**, 575.
 OSBORN, S. B., and WRIGHT, H. P. (1949) *Brit. J. Radiol.*, **22**, 110.
 SELVERSTONE, B., SOLOMON, A. K., and SWEET, W. H. (1949) *J. Amer. med. Ass.*, **140**, 277.
 STONE, P. W., and MILLER, W. B. (1949) *Proc. Soc. exp. Biol. N.Y.*, **71**, 529.
 WRIGHT, H. P. (1952) *Brit. med. Bull.*, **8**, 187.

Mr. D. M. Wallace, Joint Urological Clinic, Royal Cancer Hospital and St. Peter's and St. Paul's Hospital:

Radioisotopes in Bladder Cancer

Various radioactive isotopes having a short or long half-life can now be used as solids or in solution. These have a sufficient range of physical properties to enable practically any technique of irradiation to be carried out. In either intracavitary or interstitial irradiation the degree of penetration, the rate of dosage, the time and the protection problems for the personnel all influence the choice of isotope.

Solid Isotopes

The solid isotopes which have been used in urological practice are gold (Au^{199}), tantalum (Ta^{182}), and cobalt (Co^{60}).

Gold is used as a substitute for radon seeds in the form of a small solid cylinder of gold sheathed in platinum to filter off the beta radiation. These gold grains are much smaller than radon seeds and as they are accurately machined they can be used in a gun which permits rapid and easy insertion of the grains. The gun holds a magazine of 15 grains at one loading and the grains are ejected out of the gun by pressure on the trigger. Gold has a short half-life (2·7 days) like radon (3·8 days) but, unlike radon, if the grains are not used they can be reactivated at a nominal expense. Grains, however, have the same disadvantage as radon, the quality of an implant will be decided at the time of the implant and if over or underspaced the dose cannot be altered afterwards.

Tantalum is an alternative for radium. Used in the form of wire it is a flexible source of radiation that can be inserted by several methods. Active wire has to be sheathed in platinum, again to absorb beta radiation. When sheathed, it is flexible to a degree that varies with the thickness of the tantalum core. The wire is active along its whole length unlike radium needles, which have inactive ends. As tantalum is inert in the tissues there is no risk of absorption of tantalum from the open ends of the platinum sheath.

With a half-life of 111 days tantalum can be used over a long period of time—it can be kept as a bank and used on several occasions. If unused it can be reactivated by re-insertion in the pile. The main advantage is that linear parallel wires inserted in the bladder wall result in a more even irradiation than multiple unevenly implanted point sources and the dose can be altered by the length of time the wires are allowed to remain in situ.

The relative inexpensiveness of wire and the low wastage rate make wire an attractive alternative for radon from the administrative aspect; the ease of insertion, the quality of implant, ease of removal and its constant availability confer advantages from the clinical aspect.

Cobalt has been used as a source of radiation for a longer period than most of the other isotopes. In the form of a solid bead or needle it can be used for either intracavitary or interstitial irradiation. It has a longer half-life (5·3 years) than tantalum, but it has two disadvantages (a) it is absorbed if left in contact with the tissues, (b) it is difficult to sheath and has to be plated in order to eliminate beta radiation. Cobalt can be regarded as a substitute for radium, but it cannot be used readily as a flexible alternative.

Isotopes in Solution

Isotopes have been used in the form of solutions by various centres. Cobalt solution is still being used in other countries, but is not in use in England, because of the danger of contamination. A solution with a long half-life such as cobalt could be absorbed into the body of a patient. In the event of accidental spillage or contamination of a room, bedding, &c., there is no method of rendering the room

free from radioactivity in less than a period of years. While there are adequate alternative methods the use of cobalt in solution must be discouraged as potentially dangerous.

Sodium and bromine have both been used as solutions. Sodium (Na^{24}) as sodium chloride and bromine (Br^{82}) as calcium bromide have short half-lives (twelve hours, thirty-five hours), and any absorption or spillage is not a serious matter. Although sodium chloride is absorbed from the bladder mucosa, the rate at which this occurs is so slow that in the event of any accident it should be possible to wash out the bladder before any significant absorption has occurred.

The two solutions vary in their radiotherapeutic properties, sodium gives a relatively higher beta radiation than bromine. During treatment of a mucosal bladder lesion the respective doses would be:

Sodium 4,000 r gamma + 5,000 r beta.

Bromine 6,000 r gamma + 1,500 r beta.

These are the isotopes usually employed in urological surgery.

ISOTOPES IN BLADDER LESIONS

The lesions of the bladder for which these isotopes can be used are now well defined and fall into two main groups.

Interstitial therapy.—The single bladder tumour with minimal infiltration of the muscle wall—infiltration which, once the main tumour has been removed, is less than 1 cm. in maximum depth at any part, and where the total area of tumour and abnormal mucosa at the base is less than 5 cm. in diameter—is suitable for implantation as a single plane implant.

When a good implant is performed in this type of lesion, by whatever method, the results are excellent, but when the implant is faulty or the clinical assessment of the disease has been too optimistic the results can be very depressing.

Both gold and tantalum are still being used experimentally, but they both have advantages over radon and radium. Gold can be introduced into small lesions cystoscopically if only a few seeds are required or they can be used if there is any difficulty in inserting wire. They are, however, permanent implants and the radiation given depends solely on the quality of the implant.

Wire, after a little experience, gives a homogeneous method of irradiating a volume of tissue and the dosage can be varied depending on the length of time the wires are left in situ.

Intracavitary therapy.—The lesions suitable for intracavitary irradiation have (in our Clinic) been limited to multiple non-infiltrating mucosal carcinomatosis, a lesion that masquerades so often as papillomatosis. These lesions present as multiple small pedunculated or sessile tumours with or without areas of abnormal mucosa. The pyelogram is normal and no lesion is palpable on bimanual examination. The object of the irradiation with radioactive solutions has been to deliver sufficient radiation to the bladder mucosa yet to spare the bladder muscle as much as possible. In the early series the irradiation was given in a single dose and when using bromine in this fashion several contracted bladders were encountered. It is now given in three insertions of one to two hours and at weekly intervals, so that a total of 6000 r gamma is given over a period of fifteen days.

The technique of insertion of the balloon catheter and the method of treatment has been described in full elsewhere (Wallace, D. M., Walton, R. J. and Sinclair, W. K., 1949, *Brit. J. Urol.*, 21, 357).

A bead of cobalt at the centre of the balloon has also been used for intracavitary irradiation, but it has certain theoretical disadvantages—the point source must be kept central—a variation of one centimetre from the middle of the balloon may mean three times the irradiation on one side of the bladder compared with the opposite side. Should such a variation occur it may not necessarily be towards the tumour. Secondly the depth of irradiation is greater with a central source than with a balloon filled with solution. This is shown by the following table of depth doses.

					At surface	0.5 cm.	1 cm.	1.5 cm.
Cobalt central source	100%	80%	60%	50%
Bromine solution	100%	50%	40%	30%
Sodium solution	100%	30%	20%	15%

There is certain evidence to show that although temporary tumour regression can be obtained in infiltrating lesions, when the tumour is in muscle complete sterilization is difficult to obtain with a dose of radiation that will not destroy the whole bladder. For this reason intracavitary irradiation should be confined to lesions that have not spread clinically into muscle. It should not be used in cases of low-grade papillary carcinomatosis that can be adequately controlled by repeated diathermy. Provided the histology is representative, and the tumours do not undergo mutation, the natural history of such tumours is such that they are unlikely to shorten the patient's life. For the average or high-grade tumours where infiltration is likely to occur the risk of intracavitary treatment is justified as an alternative to cystectomy.

The late complications of treatment have been minimized by adopting a technique of fractionating the doses, but although as yet with this technique no bladders have had to be removed nor ureters

transplanted, considerable urinary frequency and sloughing of the bladder mucosa may result three to six months after treatment.

After a year the histological changes in the bladder wall are those of atrophic mucosa—numerous capillaries in the submucosa and a loss of muscle in the media of the arterioles. Cystoscopically telangiectases appear and hæmaturia may occur in the absence of any visible tumour. It is at this stage that diathermy is apt to lead to a necrosis which may be painful and result in extreme frequency of micturition.

The most important complication is the development of fresh tumours months or years after irradiation. These may be recurrences—evidence of incomplete tumour sterilization, or they may be further primary tumours—the manifestation of the presence of carcinogenic factors in the urine. If this should prove to be the case then the only curative treatment must be either in biochemistry or in radical surgery.

Results obtained by radioactive isotopes:

(1) *Interstitial tantalum implants:*

Longest case-survival	2 years	
Total number treated		25
Dead of intercurrent disease		2
embolism 1		
cerebral hæmorrhage 1		
Alive with bony metastases		1
Alive and tumour free		22

(2) *Intracavitary irradiation with sodium²⁴ and bromine⁸² solution:*

Longest case-survival	3½ years	
Total number treated		58
Died from cancer		7
Died of intercurrent disease		3
Total cystectomy for residual tumour		7
Transplant for contracted bladder		3
Died from renal failure		3
Alive with functioning bladder and tumour free		29
Alive with tumour recurrence or second primary		6

Mr. Selwyn Taylor,¹ Postgraduate Medical School of London:

Radioactive Iodine

As a surgeon with a particular interest in the thyroid gland, the isotope with which I have been most concerned is radioactive iodine.

The same general principles apply to the use of any radioactive isotope in biological studies. It can be employed for three main purposes: to trace, to measure and to treat by irradiation. Radioiodine can be used in each of these ways.

Tracer techniques offer a unique method of investigation since radioiodine is accepted by the tissues in exactly the same way as stable iodine. Moreover, even when present in the most minute amounts it can be detected and measured by reason of its radioactive emanations.

Measurement in such work can be carried out in three very different ways: first, *in vitro*: for example, the measurement of activity in urine or serum removed from the patient. Second, *in vivo*: for example, a counter can be placed over the patient's neck for the detection of gamma rays. Third, the distribution of the radioactive isotope can be demonstrated in tissue removed from the body: for example, if an ordinary histological section of the thyroid gland containing radioiodine be placed in contact with photographic film, the blackening on the latter will demonstrate the actual site of the isotope in the tissues. Such a picture is called an autoradiogram.

Tests of Thyroid Function

There are many tests of thyroid function; for example the B.M.R., sleeping pulse rate, plasma cholesterol, and creatine excretion. Each provides valuable information and throws light on a different facet of a process which involves the metabolism of every cell in the body. Radioiodine can be used as a direct measure of thyroid function by tracing the metabolism of iodine in the gland and has the additional merit of being largely free from the subjective errors of clinical judgment.

So many tests of thyroid function have been devised using radioiodine that it will simplify matters by first describing how iodine circulates in the body. When a tracer dose of radioiodine by mouth is given it is rapidly absorbed and mixes with the iodine already in the plasma. It is selectively trapped by the thyroid where it is built up into thyroxine and stored as colloid in the follicles. The kidneys excrete their share in the urine. Part is discharged from the follicles into the plasma where it circulates as hormonal or protein-bound iodine. The circulating hormonal iodine is broken down in the tissues, mainly the muscles, and part of the iodine so released passes to the thyroid once more, part goes through

¹ In receipt of a grant from the Medical Research Council.

the liver
three d
may be
iodine
hormon
thyroxin

Hyp
longer
are con
some o
every g
40% of
accordi

A m
of the n
of iodic
the plas
taking

As a
much t
thyroid
drinks
three p
obtaine
To re
thigh o
paratus
alternat
euthyrc

If a C
area it
elsewhe
of the t
into the

One
routine
forty-ei
counter
held ov
are ther
function
a norma
1951. L
nodule"
which t
associat
that sul

There
thiourac
my own
with pre
living fa
continua

Radi
drink a
appari
formly
risk to c
So muc
the dose
experier

the liver to the gut and is reabsorbed, while some is excreted in the urine. There are, therefore, at least three different ways of measuring the overall thyroid function with radioiodine. A Geiger counter may be placed over the neck to record the uptake directly. The urine can be collected and its radioiodine content will give an indirect measure of the thyroid uptake. Or thirdly, the concentration of hormonal radioiodine in the plasma may be determined as a measure of the rate of production of thyroxine. Combinations of two of these are often the most useful.

Hyperthyroid patients show a more rapid accumulation of the isotope and retain larger amounts for longer periods than normal. Hypothyroid patients usually show a diminished uptake. When the results are compared with those obtained from clinically normal or euthyroid individuals, there is usually some overlap but this is not surprising since hyper- and hypo-thyroidism are not sharply defined and every gradation exists between them and the euthyroid state. Most normal people take up less than 40% of a tracer dose in the first forty-eight hours and hyperthyroid patients amounts of over 60%, according to the severity of their disease.

A more accurate estimate of thyroid function is obtained by making simultaneous determinations of the radioiodine concentration in the gland and in the plasma. Then the volume of plasma cleared of iodide per minute, i.e. the "clearance rate," is obtained by dividing the uptake over the neck, by the plasma level. In normal people it is about 20 c.c. per minute. Since this technique requires the taking of serial blood samples it has been found simpler to compare counts over the neck and the thigh.

As a routine diagnostic test, serial measurements over the neck and thigh of the patient take up much time and can only be done in limited numbers. For this reason indirect measurements of thyroid function made by collecting the urine after a tracer dose, have some advantage. The patient drinks 10 μ c. and is sent away from hospital with containers for the collection of urine. If at least three periods are taken over a total time of not less than forty-eight hours, good discrimination is obtained between hyperthyroid and euthyroid individuals.

To recapitulate, thyroid function can be accurately determined by measurements over the neck and thigh or neck and plasma, but when it is difficult to bring the patient to the necessary counting apparatus, or where large numbers of patients are involved, urinary excretion tests offer an excellent alternative. Whichever method is employed it is first necessary to carry it out on a wide selection of euthyroid individuals to discover the range of normality for the particular test.

Localization Studies

If a Geiger tube is shielded with lead in such a way that it only records the emanations from a tiny area it becomes possible to map out the position and intensity of iodine uptake over the neck and elsewhere. This can be of value to the surgeon since all the thyroid tissue may be situated at the back of the tongue or along the course of the thyroglossal tract, or an enlarged thyroid may extend deeply into the mediastinum.

One of the most useful aids to diagnosis has been a careful method of scanning which we now use routinely before operating on a goitre. The patient receives a tracer dose of 100 μ c. and thirty-six to forty-eight hours later a perspex grid marked in 1 cm. squares is placed over the neck. A special counter with lead shield and central lead core, so designed that it only records parallel rays, is then held over each square for 1 to 2 minutes. The counts, expressed as a percentage of the tracer dose, are then plotted on graph paper and if lines are drawn through areas of equal iodine uptake a chart of function is obtained. These lines, which resemble the isobars of the meteorologist, produce a chart in a normal patient which resembles closely the anatomy of the gland (see Taylor, S., and Stewart, F. S., 1951, *Lancet*, ii, 232). A nodule in which no radioiodine is taken up is usually referred to as a "cold nodule" and if solitary and in a young patient might raise the suspicion of malignant disease. A nodule which takes up more radioiodine than the surrounding tissue is referred to as a "hot nodule" and if associated with hyperthyroidism indicates that removal of the nodule will relieve the condition and that subtotal thyroidectomy is unnecessary.

Isotope Therapy of Hyperthyroidism

There are three very different methods available today for treating hyperthyroidism: thyroidectomy, thiouracil and radioactive iodine. The indications for each are slowly emerging but I shall state only my own particular preferences. Surgery is necessary for all toxic nodular goitres, very large goitres with pressure on the trachea, those who develop sensitivity to the thiouracil drugs and patients normally living far removed from hospital. Thiouracil is most valuable in pre-operative preparation but when continued for long periods may induce a remission.

Radioiodine is much the kindest treatment from the patients' point of view. They have only to drink a little tasteless fluid and the hyperthyroidism is gradually controlled, the maximum improvement appearing in about two to three months. Graves' disease or hyperthyroidism associated with a uniformly enlarged gland responds best; toxic nodular goitres are more resistant. There is no anaesthetic risk to contend with, no haemorrhage, no risk of damage to the recurrent nerve or to the parathyroids. So much for the credit side of the account. The debit side is less clearly defined. In the first place the dose is calculated on the number of grammes of thyroid tissue estimated clinically. Even the most experienced thyroidologist can be 100% wrong on this score. Next, it is assumed that uptake is uni-

formly spread throughout the gland; autoradiograms, however, show a patchy uptake. Finally, there is the fear that the intense irradiation may induce a malignant change, possibly after a long latent period. As a corollary, the production of skin cancer after a latent period of twenty years or more following X-ray therapy may be quoted. In the experimental rat, radioiodine certainly produces thyroid cancer when combined with prolonged thiouracil therapy. In brief, radioiodine is of most value for recurrent hyperthyroidism, especially when previous operation has paralysed a vocal cord, for older patients with severe heart disease and those who cannot be prepared for surgery, and for patients with severe exophthalmos in whom thyroidectomy may precipitate corneal ulceration. The question whether or not radioiodine will produce thyroid cancer in man must go unanswered until more years have elapsed. For the present I am unwilling to recommend this form of therapy in anyone with an expectation of life of more than 20 years if suitable alternative therapy is available.

Autoradiography

A most convincing proof of the metabolism of iodine in the thyroid is provided by autoradiography and in combination with histology it has proved much that of necessity had previously been speculative and added some entirely new knowledge. The technique I have adopted in investigating the last 60 patients with goitre submitted to operation is as follows:

The patient is given 100 μ c. of radioiodine on a fasting stomach and the urine collected in three periods over the subsequent forty-eight hours as a measure of total thyroid function. After thirty-six hours the neck is scanned and a map of iodine uptake obtained as a guide to what should be excised. After operation, the tissue is weighed and sections made through whole lobes in the plane thought most likely to provide useful information. The tissue is difficult to process but sections are prepared on a sledge microtome and left in contact with X-ray film which is then developed.

Mr. Selwyn Taylor then showed lantern slides prepared by mounting the actual histological preparation alongside the autoradiograph. The preparations illustrated the evolution of nodular goitre (see Taylor, S., 1952, *Lancet*, i, 175).

Mr. R. J. Walton, Radiotherapist, Royal Cancer Hospital, London:

Clinical Uses of Radioactive Colloidal Gold

Radioactive gold (Au^{198}) is prepared by exposure of normal gold to neutron bombardment in the atomic pile. It emits a beta radiation of 0.96 MeV energy and a gamma radiation of 0.41 MeV and decays with a half-life of 2.7 days. It can be easily prepared as a colloidal solution having an average particle size of about 100 $m\mu$. In this form it has been used clinically in two main ways:

The first of these has been in the relief of symptoms resulting from the formation of malignant pleural and peritoneal effusions. The technique of administration is simple, 100 ml. or so of the fluid of activity 80–120 mc. being run into the cavity concerned at the end of normal paracentesis, the patient being postured to facilitate free dispersal throughout the cavity. Nausea and vomiting of variable severity are experienced in some cases for twenty-four hours or so and a few patients have complained of gastro-intestinal upset lasting two or more weeks. About half of the patients treated have received benefit from the treatment by a slowing down or temporary complete cessation of fluid formation, and I feel that the method is a useful palliative one in this late and distressing stage of malignant disease.

The second therapeutic use of radioactive colloidal gold has been reported principally from the United States of America. The neoplastic tissue is directly infiltrated with Au^{198} ; the amount necessary to deliver a pre-determined dose of radiation (mostly due to beta rays) is calculated from the volume of the tumour. A technique of multiple injections coupled with the use of hyaluronidase seems to result in fairly even dispersal of the active material. Tumours of the face, breast and parametrium have frequently been treated in this way, while more recently the technique has been extended to include the prostate. Successful treatment is said to result in rapid shrinkage of the tumour mass and its replacement by fibrous tissue.



FIG. 1.—
depth

tending
of the
of Sub
chronic
of the
over se
of the
dose of
1 Wor
Apar

Section of Experimental Medicine and Therapeutics

President—Professor R. V. CHRISTIE, M.Sc.McGill, D.Sc.Lond., M.D., F.R.C.P.

[October 14, 1952]

DISCUSSION ON THE RADIATION SYNDROME

Dr. W. M. Court Brown¹, and Dr. R. F. Mahler¹, Department of Medicine, Postgraduate Medical School of London, Hammersmith Hospital, London:

Some Clinical and Biochemical Observations Following a Single Therapeutic Dose of X-rays

Introduction.—Following a single dose of X- or γ -rays, substantially larger than can be given under clinical conditions, a series of events occurs which is collectively known as The General Radiation Syndrome (Fig. 1). These events are grouped into four periods: The Period of Initial Reaction which starts after a latent period of about two hours after exposure, and is characterized by nausea, vomiting and fatigue; The Period of Acute Reaction, which develops towards the end of the second week,

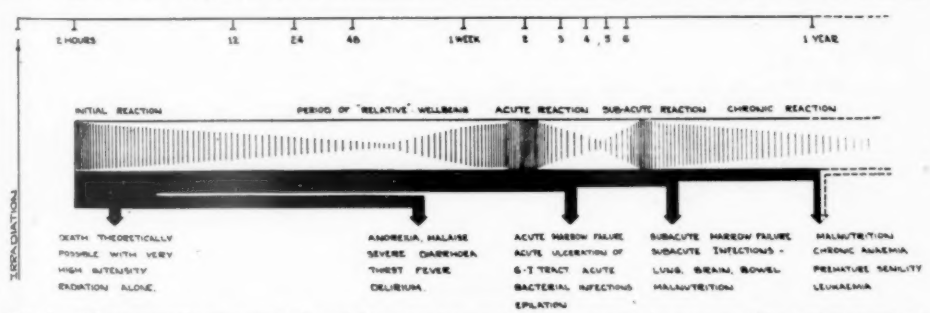


FIG. 1.—Diagrammatic representation of the complete radiation syndrome in man and the stages at which death commonly occurs. Adapted from Liebow, Warren, and De Coursey, *Amer. J. Path.*, 1949, **25**, 853.

tending to become maximal over the third and fourth weeks, and which is characterized by ulceration of the gastro-intestinal tract, acute marrow failure, bacterial infections, and epilation; The Period of Subacute Reaction, which supervenes towards the end of the sixth week and during which more chronic forms of infection become manifest, such as lung and brain abscesses, and chronic ulceration of the bowel; The Period of Chronic Reaction, which may last for a long period of time, possibly over several years, during which anæmia and malnutrition are outstanding features, with the possibility of the development of leukæmia. Whilst species differences exist, particularly concerning the critical dose of radiation required to produce the full syndrome, these findings are remarkably comparable

¹Working for the Medical Research Council.
AFFILI—EXPER. MED. 1

over quite a range of different mammalian types, such as the mouse, rat, dog, rabbit, pig and goat. In addition, the experiences of Nagasaki and Hiroshima [1], and the recently reported findings in some individuals accidentally exposed during the explosion of a nuclear reactor at Los Alamos [2], indicate that man also under these circumstances shows the characteristic features of the General Radiation Syndrome.

The studies we wish to report were carried out on patients who had been referred for radiotherapy and they have demonstrated a pattern of symptoms which is a milder version of the Period of Initial Reaction of the General Radiation Syndrome.

The symptom pattern following a single therapeutic dose of X-rays.—The response to a single dose of X-rays has been studied in 50 patients referred for X-ray therapy to the Department of Radiotherapy, Hammersmith Hospital. The patients chosen were those whose disease conditions necessitated the irradiation of large volumes of tissue and whose general health was good. Dosage has been expressed in megagramme-roentgens rather than the conventional "r" units of dose, as the use of the megagramme-roentgen, an index of the total amount of energy absorbed by the body, should facilitate the comparison of the effects of the irradiation of different anatomical sites. The chief sites of irradiation were the whole length of the spine, the upper half of the trunk, and the abdomen. The mean dose to the first two sites was 3.9 megagramme-roentgens and to the abdomen 3.3 megagramme-roentgens.

The pattern of events following such a dose of X-rays was found to consist of, firstly, a latent period before any symptoms commenced, secondly a period of acute disturbance, and finally a period of recovery. The mean length of the latent period, considering the whole group of patients, was nearly two and three-quarter hours. When a comparison was made between those patients who were most severely upset and who vomited, and those who were less upset and did not vomit, the mean length of the latent period was found to be shorter in the first group than in the second group, the difference being approximately three-quarters of an hour. This difference was found to be statistically significant and was not influenced by such considerations as dosage, age, sex or disease in our group of patients. This finding indicates that, with a constant dose of X-rays, symptoms are likely to develop at an earlier stage in the more sensitive patient than in the patient with a greater degree of resistance.

The latent period terminates with the sudden onset of symptoms, the outstanding complaints at this time being fatigue, anorexia and nausea, and these remain present for at least an hour before subsiding, in those patients who are only mildly upset. Where the period of acute disturbance is more severe, after about an hour the fatigue and nausea become accentuated, and in some instances vomiting and retching supervene. One bout of vomiting may occur, or vomiting may occur at intervals for two to three hours in the most severely upset patients before the recovery period ensues.

Dependent on the degree of upset in the period of acute disturbance, the recovery phase may last less than one day or for as long as five days. During this phase there is a gradual disappearance of firstly nausea, then fatigue and finally anorexia.

Objective assessment of such symptoms as fatigue, anorexia and nausea is practically impossible but we have a very strong subjective impression that the fatigue experienced is in some way dissociated from the nausea and anorexia. Thus in some patients fatigue has been undoubtedly the only symptom, whilst in others it is certainly the predominant symptom, nausea and anorexia being only fleeting complaints and vomiting not occurring at all. At the other end of the scale, a group of patients has been collected in whom nausea and repeated vomiting were the only complaints. It was also remarkable in these latter patients that, almost immediately after the vomiting had ceased, the patients were symptom-free. It appears also from studies which have been carried out into electrolyte excretion that certain changes are related to the symptom of fatigue and are absent when fatigue is absent, even though nausea and vomiting occur. These impressions suggest that two disorders underlie these symptoms, one associated with fatigue and the other with nausea and vomiting.

34 of the 50 patients observed were also subjected to sham irradiations to control the possible effects of emotional and psychological disturbances in producing symptoms. 8 of these patients developed symptoms, as opposed to 46 out of the 50 exposed to the actual irradiation, and in all instances the symptoms lacked the characteristic pattern and timing of those following the real irradiation.

Clinical observations on blood-pressure changes, pulse-rate and respiratory rate have not shown any consistent changes until vomiting supervenes.

Changes in the peripheral blood count.—The outstanding features of the haematological response are the changes found in the total white cells and differential counts; no significant changes have been noted in the red cell counts and haemoglobin levels, or in the osmotic fragility of the red cells or in the blood heparin levels. In most patients there is an increase in the total white cell count at the time of onset of the symptoms, the rise being due to a neutrophil leucocytosis without a change in the lymphocyte count. Thereafter, commencing at the end of the first day or during the second day the white count falls, due to a drop in both the neutrophil and lymphocyte fractions, and in the most severely upset patients it reaches its maximum depression between the seventh and twelfth days. It will be noted that this time of maximum depression agrees closely with the time at which the Period of Acute Reaction of the General Radiation Syndrome would have become clinically manifest had the X-ray dosage been very much greater. There does appear also to be a definite correlation between the degree of symptomatic upset and the level to which the total white cell count falls (Table I).

TABLE I.

Day 0†

1

2

3

4

5

6

7

8

9

10

*All

†Th

Chan
carry on
to main
and, of
vomitin
and the
with rac

Cas

Day

-3

-2

-1

0*

+1

+2

+3

+4

+5

+6

*Irr

†Th

Ur

ind

the sodi
hours al
drops a
states a
there ap
balance,
outstanc
Furth

TABLE I.—THE EFFECT OF A SINGLE DOSE OF X-RAYS ON THE TOTAL WHITE CELL COUNT IN RELATION TO THE TOTAL DURATION OF SYMPTOMATIC UPSET

	Case No. 34/51. Ankylosing spondylitis. Whole spine irradiation. Integral dose = 4.2 megagm. r	Case No. 1/50. Ankylosing spondylitis. Whole spine irradiation. Integral dose = 3.9 megagm. r	Case No. 4/51. Ankylosing spondylitis. Whole spine irradiation. Integral dose = 4.0 megagm. r
	Mean of 6 control values = 8.68* 95% confidence limits 9.30-8.06	Mean of 3 control values = 8.7* 95% confidence limits 9.37-8.03	Mean of 6 control values = 5.6* 95% confidence limits 6.56-4.64
Day 0†	8.9	11.0	6.0
1	8.8	9.0	9.0
2	—	9.0	6.0
3	5.05	—	—
4	5.5	8.0	6.0
5	4.5	7.0	5.0
6	5.5	6.0	—
7	4.6	6.0	5.0
8	3.5	—	4.4
9	—	—	4.5
10	4.6	—	4.4

*All values in cells per c.mm $\times 10^3$.

†The blood counts on Day 0 were done approximately four hours after the commencement of irradiation.

Changes in water and electrolyte excretion.—In a number of patients attempts have been made to carry out daily water and electrolyte balances. In many of these patients it has been quite impossible to maintain a reasonably constant intake of food on the day in which the symptoms are maximal, and, of course, in a number of patients the position has been further complicated by the presence of vomiting. However, in a small number of individuals a fairly constant food intake has been achieved and these studies do indicate that a negative state of salt and water balance is frequently associated with radiation sickness (Table II). In the most severely upset patients the negative balance as regards

TABLE II

Case No. 7/51: Benign Menopausal Bleeding. Single X-ray Treatment to Pelvis, Using Opposed 15×10 cm. Fields. Integral Dose = 6.24 megagm. r

Day	Chloride (meq/24 hrs.)			Water (mls./24 hrs.)			Weight (kilo)	Remarks
	Intake	Output	Balance	Intake	Output	Balance†		
-3	113	114	- 1	2,557	1,480	+1077	75.2	
-2	110	104	+ 6	2,226	1,350	+1011	75.1	
-1	116	103	+13	2,661	1,295	+1366	75.2	
0*	116	140	-24	2,481	1,430	+1051	75.3	Fatigue and nausea
+1	101	145	-44	1,938	1,535	+ 403	74.6	Fatigue and anorexia
+2	103	117	-14	2,354	1,330	+1024	74.7	Fatigue
+3	97	75	+22	2,198	940	+1258	74.6	Anorexia
+4	108	95	+13	2,593	1,730	+ 863	74.6	Mild anorexia
+5	111	99	+12	2,205	1,375	+ 830	75.2	
+6	115	99	+16	2,635	1,525	+1110	75.3	

*Irradiation given at beginning of Day 0.

†The water balance has been derived from the total water intake and the volume of urine excreted. Under these conditions and provided that the weight is steady, the apparent positive balance is an index of the insensible water loss via lungs, skin and bowel.

the sodium and chloride ions may amount to 100 milli-equivalents or more in the first twenty-four hours after irradiation, but these, of course, are just the patients whose food intake, try as one may, drops acutely during this period. The overall picture, however, indicates that these negative balance states are true, although in the majority of instances not the actual quantities involved. Furthermore, there appears to be a correlation between the symptom of fatigue and the negative salt and water balance, the negative balance being at its greatest in those patients in whom severe fatigue was the outstanding complaint.

Further insight into this negative balance state is obtained by considering the results in a patient

who was maintained on the Borst Régime of four-hourly milk and biscuit feeds (Fig. 2). It is seen that during the first four hours after irradiation there is a small but significant increase in urine flow as compared with the corresponding control periods, and that during the eight hours after irradiation there was a significant increase in the amount of chloride lost in the urine. (In the right half of Fig. 2 the means of the values for the urine volume and the urine chloride excretion for each corresponding four-hourly period during the four days preceding irradiation are shown in blocks delineated by interrupted lines, and, in addition, the values of twice the standard errors of these means. The values observed for each period on the day of irradiation are indicated in solid lines.) The total duration of

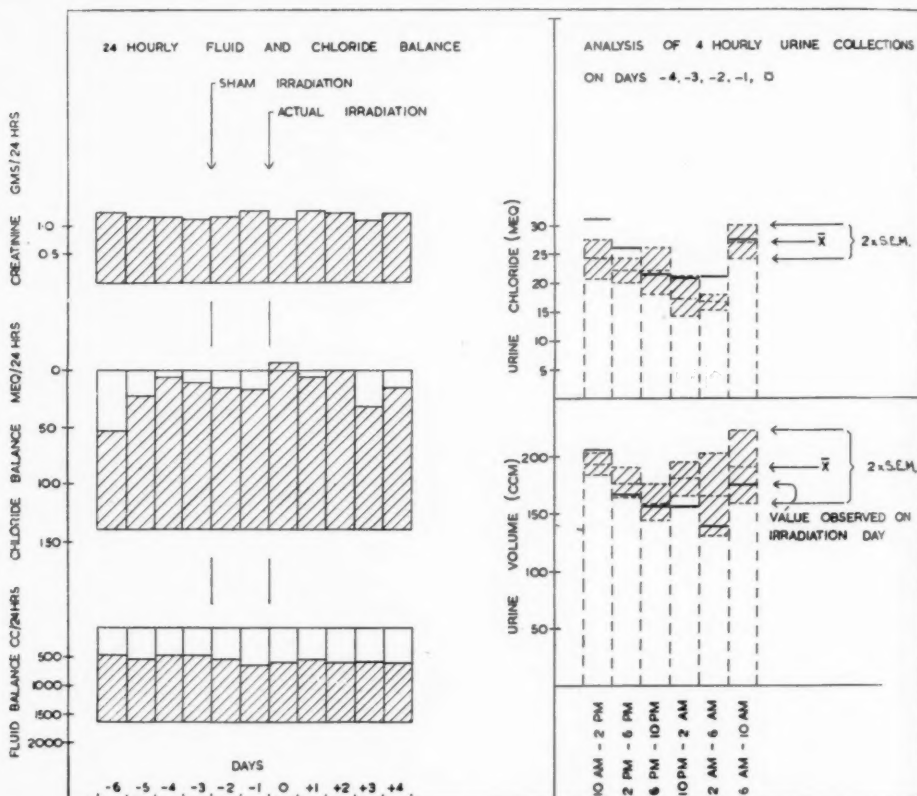


FIG. 2 (Case No. 19/51).—Generalized reticulosis. Whole body irradiation. Four-hourly milk and biscuit feeds. $\Sigma = 2$ megam r.

symptoms in this patient was extremely short, of the order of one hour, and the symptoms themselves were very mild, amounting to no more than some slight fatigue and transient anorexia. The changes in this patient are so slight that it is only by adopting this method of search that they can be demonstrated; on the other hand it is practically only in this type of very mild disturbance that an absolutely steady food intake can be achieved.

Following the demonstration of this type of change in water and chloride excretion, more detailed attention has been paid to the changes occurring in the urine and plasma over the first four or five hours after irradiation.

Urine collections have been made at approximately half-hourly intervals, the collections commencing some two hours before irradiation and being continued as long as possible after symptoms had supervened. The majority of the patients so examined have been catheterized and in a fasting state, and the collections have been made during the afternoon to avoid any naturally occurring peak of electrolyte excretion. In a minority of patients, catheterization has not been possible and some have not been fasting. This latter group, however, have demonstrated the same type of changes at the same time as

the cath tends to by a rise an actu

Caso

Collection No.
1
2
3
4
5*
6
7
8+
9
10+

behavior be a gen as a sym rate asso change i After measure has not filtration been rea be in th studies. of urine irradiati

We ha phospho quite ste may be relatively some pa percenta the perio in the pr reabsorb

Finaly filtration be criti techniq to the Depart metabo evidenc time th

In co of X-ray APRIL

the catheterized fasting group. We have found that associated with the onset of symptoms there tends to be a rise in the excretion rates of sodium, chloride and phosphorus frequently accompanied by a rise in the rate of urine flow, associated with either no fall in the urine specific gravity or even an actual rise (Table III). Concomitant with these changes there is often a rise in urine pH. The

TABLE III

Case No. 49/52: Ankylosing Spondylitis. Single X-ray Treatment to Whole Length of Spine.
Integral Dose = 4.82 megam. r

Collection No.	Time (min.)	Urine values						Plasma values (m eq/L)					
		Flow rate (ml/min.)	Specific gravity	Na μ eq/min.	K μ eq/min.	Cl μ eq/min.	P μ eq/min.	Creatinine mg/min.	Na	K	Cl	P	HCO ₃
1	26	4.1	1010	216	58	208	138	—	133	4.1	93	2.3	28.0
2	34	2.2	1013	207	70	205	51	1.36	—	—	—	—	—
3	25	1.5	1017	198	77	179	31	1.18	137	4.3	93	2.0	31.0
4	43	1.0	1018	156	63	130	21	0.88	—	—	—	—	—
5*	40	2.4	1012	216	47	170	29	1.45	—	—	—	—	—
6	35	0.9	1015	95	20	70	20	0.74	137	4.4	94	2.2	28.8
7	34	1.3	1013	187	20	140	38	0.80	139	—	97	2.3	28.0
8†	35	2.4	1015	334	47	280	69	0.70	137	4.5	95	2.2	26.7
9	32	1.3	1018	259	43	240	59	0.80	137	4.4	96	2.4	27.6
10‡	26	0.4	—	45	20	—	26	0.40	138	—	96	2.3	26.3

*Collection during period of irradiation.

†Onset of symptoms.

‡Onset of vomiting.

behaviour of potassium is variable. As was found in the daily balance studies, there again seems to be a general correlation between the degree to which these changes occur and the incidence of fatigue as a symptom. At one end of the scale one may find a rise of 50% or more in the sodium excretion rate associated with marked fatigue, in contrast to the absence of any significant sodium excretion change in the group of patients who simply suffer from nausea and vomiting.

After these changes have developed and when vomiting occurs, the glomerular filtration rate, as measured by creatinine, tends to fall and the electrolyte excretion rates drop to very low levels. It has not been possible for us to continue these observations to the point at which the glomerular filtration rate completely recovers. It would be very interesting to know whether, after this point has been reached, electrolyte excretion is re-established at an abnormally high rate, as presumably it must be in the severely upset patients, in view of the negative balances shown in the twenty-four-hourly studies. (It will be noted in Table III that during the period of irradiation there is a rise in the rate of urine flow, associated with a fall in specific gravity. This change has been frequently noted during irradiation and is considered to be due to emotional causes.)

We have not been able to find any consistent changes in the plasma levels of sodium, chloride and phosphorus at the time these urinary changes are occurring. In fact, the plasma levels usually remain quite steady over the period of observation. However, increases in the urinary electrolyte excretion may be due to small increases in the plasma load not great enough to be demonstrated by the existing relatively inaccurate techniques of biochemical analysis. Against this explanation is the fact that in some patients calculations of the amount of phosphorus reabsorbed in the proximal tubule as a percentage of the total filtered phosphorus have indicated decreases of the order of 10-15% during the period of commencement of symptoms, indicating that there has been some functional change in the proximal renal tubule. Similar calculations have indicated decreases in the amount of sodium reabsorbed and these findings may correlate directly with the observed increases in urine flow.

Finally, part of the increased electrolyte excretion may be the result of changes in the glomerular filtration rate. The use of creatinine clearances as an index of glomerular filtration rate can, of course, be criticized but we have felt that the measurement of inulin clearances with a constant infusion technique is not possible in these patients owing to the prolonged period of observation required and to the fact that the patients have to be moved quite a distance from the ward to the Radiotherapy Department and back again. Changes in the glomerular filtration rate may occur in response to metabolites liberated from damaged tissue, and if we are to judge by the results of animal investigations, evidence of cell death is almost certainly present in the radiosensitive tissues of our patients at the time these changes occur.

In conclusion, it is hoped that this brief review of what we believe to be the effects of a single dose of X-rays within therapeutic limits will stimulate further investigations upon similar lines. The

problems associated with the physiological changes produced by X-rays are bound to be complex in view of the wide possible range of disturbances that may be produced in many fundamental biological systems during the period of irradiation. Detailed observations in man following a single therapeutic dose of X-rays may allow us to bridge the gap between clinical radiation sickness and the General Radiation Syndrome in animals, and it may well be that such human studies will allow us to make some observations with greater ease at a period in time more closely related to the initial tissue reactions produced during irradiation than can be achieved in animals.

ACKNOWLEDGMENTS

We wish to acknowledge our indebtedness to Professor J. McMichael and Dr. Russell Fraser for their advice and criticism during this investigation and the preparation of this paper.

REFERENCES

- 1 LIEBOW, A. A., WARREN, S., and DE COURSEY, E. (1949) *Amer. J. Path.*, **25**, 853.
- 2 HEMPELMANN, L. H., LISCO, H., and HOFFMANN, J. G. (1952) *Ann. intern. Med.*, **36**, 279.

Dr. R. H. Mole and Dr. Olga D. Batt, M.R.C. Radiobiological Research Unit, A.E.R.E., Harwell:

Iodide Metabolism

Irradiated animals lose weight, have an increased basal oxygen consumption, and can be protected to some extent against the effects of irradiation by SH compounds like thiourea. Irradiated female rats, however, do not show any evidence of increased thyroid activity. The rate of uptake of iodine by the thyroid, as determined after administration of radioactive iodide, is decreased to about one-quarter of normal. This marked decrease is first evident on the third day after 800 r, the dose which kills over 90% of the rat stock used, and persists for about a week, i.e. until all the animals have died. After 600 r, which kills less than 10% of the rats, the decrease in iodine uptake by the thyroid occurs on the third day also, but the uptake returns to normal by the seventh day. The depression in iodide uptake agrees with the histological findings of Betz (1952) but he found evidence of increased cellular activity in the thyroid at later times after sublethal doses which we did not detect radiochemically.

The reason for the decreased uptake is not clear. It is first seen on the third day when diarrhoea first becomes a symptom, when the hæmatocrit reading is raised, and when the adrenal gland is hypertrophying. The first two findings suggest that there may be a circulatory deficiency following fluid loss from the bowel, but circulatory factors are not often considered in discussions on thyroid function. Further the diarrhoea has cleared up by the sixth day after 800 r though thyroid function continues to be depressed.

However, *in vitro* Warburg studies failed to reveal any striking differences in the ability of thyroid glands from normal and irradiated rats to concentrate iodide, which perhaps supports the hypothesis that the depression of thyroid function *in vivo* is due to some extrathyroidal factor.

Renal excretion of iodide is depressed about the same time after whole body irradiation as thyroid uptake and to a much greater degree. Renal clearance of iodide recovers after 600 r and continues to be depressed after 800 r just as is thyroid clearance, but less consistently.

REFERENCE

- BETZ, H. (1952) *C. R. Soc. Biol.*, **146**, 315.

Mrs. Philippa H. Herbert and Dr. R. H. Mole, M.R.C. Radiobiological Research Unit, A.E.R.E., Harwell:

Adrenal Cortical Function and Tissue Glycogen

Our studies, *inter alia*, of glycogen and glucose in tissues of normal and adrenalectomized rats examined under carefully controlled conditions, conflict in some respects with the findings of other workers. Twenty-four and forty-eight hours after a superlethal dose of whole body X-irradiation (1,000 r) there was increased adrenal activity as found by Edelmann (1948), North and Nims (1949), McKee (1952), but this hyperactivity did not diminish on the third day as reported by Edelmann and Nims (1950). It is on the third day that there is a marked increase in adrenal weight (Patt, Swift, Tyree and John, 1947; Anderson, Blaschko, Burn and Mole, 1951).

Twenty-four hours after 600 r there was no evidence of adrenal hyperactivity but from the second to fourth days there was a marked rise in liver glycogen prevented by adrenalectomy. The absence of adrenal hyperactivity twenty-four hours after 600 r must mean that any initial stimulus produced by radiation is transient. The major activity occurs as a delayed reaction reaching its height about the

time when
situation
activity fo
and Kats
after irra
So far
sugar aft

ANDER
EDELMA

McKEE
NORTH
PATT, H

Dr. D. W

One ca
the energ
very sens
the radiat

Howev
for insta
radicles
inhibit th

As one
methods
(1949) in
X-irradi
after an
spleens o

It is w
process
animal t

Protect
have use
240 kV.
very stee
950 r or
mouse s
anæsthe

A-G
had had
immedi
experim
for Cl
may be

time when the rats are in the early acute phase of post-irradiation sickness. Radiation is a "stress-situation" (Patt *et al.*, 1947) but this seems to be a relatively unimportant cause of the adrenal hyperactivity following whole body irradiation. This conclusion is supported by our finding, unlike Edelmann and Katsh (1952), that adrenalectomy did not seem to affect survival until after the first two days after irradiation.

So far it has not been possible to account for the observed changes in tissue glycogen and blood sugar after irradiation without assuming some factor additional to increased adrenal activity.

REFERENCES

- ANDERSON, C. T., BLASCHKO, H., BURN, J. H., and MOLE, R. H. (1951) *Brit. J. Pharmacol.*, **6**, 342.
 EDELMANN, A. (1948) B.N.L. C-4. Brookhaven National Laboratory Conference Report. Upton, N.Y.
 —, and KATSH, S. (1952) *Amer. J. Physiol.*, **168**, 626.
 —, and NIMS, L. F. (1950) B.N.L. 51. Brookhaven National Laboratory Quarterly Report. Upton, N.Y.
 McKEE, R. W. (1952) *Fed. Proc.*, **11**, 256.
 NORTH, N., and NIMS, L. F. (1949) *Fed. Proc.*, **8**, 119.
 PATT, H. M., SWIFT, M. N., TYREE, E. B., and JOHN, E. S. (1947) *Amer. J. Physiol.*, **150**, 480.

Dr. D. W. H. Barnes, and Dr. J. F. Loutit, M.R.C. Radiobiological Research Unit, A.E.R.E., Harwell:

Protective Effects of Implants of Splenic Tissue

One can conceive of the action of ionizing radiation on living tissues being purely physical. Thus the energy might be wholly expended in breaking valence linkages of complex essential molecules in very sensitive target areas. If this were so protection would be limited (as it is at present) to preventing the radiation from reaching tissue by shields of lead, concrete or other suitable material.

However, radiation may also exert some effect indirectly through chemical effects. There is evidence for instance that X and γ rays can produce from water, the main constituent of the body, oxidizing radicals such as OH, HO₂ and even H₂O₂. By means of suitable medication one should be able to inhibit the deleterious effect of these oxidizing agents and this, in fact, has been done.

As one can influence this effect by chemical means, it should also be possible to do it by biological methods, even if all the intermediate chemical steps are not understood. Jacobson and his co-workers (1949) in Chicago have already shown that by protecting the spleen of a mouse with lead during X-irradiation its chance of survival is greatly increased. Furthermore, they (1951) showed that even after an otherwise lethal dose, mice could be saved by the insertion into the peritoneal cavity of spleens of normal infant mice.

It is with this last proposition that we wish to deal. Its potential practical value is obvious: it is a process of therapy not prophylaxis and in terms of function it is an alteration of the reactivity of the animal to injury, not a modification of the injury.

Protective effects of implants of splenic tissue.—To confirm the findings of the Chicago group, we have used mice from our inbred CBA stock. The M.L.D. (thirty days) for this strain for X-rays 240 kV. 15 ma. H.V.L. 1.2 mm. Cu at 42 r/min. is approximately 800 r; the dose-mortality graph is very steep rising from zero at 725 to 100% at 850 r (Mole, R. H., 1950). The working dose chosen was 950 r or about 100 r greater than the normal 100% lethal. The probability of any single untreated mouse surviving this dose is less than 0.01. Control mice in each experiment had operative and anaesthetic insults similar to the experimental animals. Table I shows that in the seven experiments

TABLE I.—SURVIVAL OF MICE (950 r) GIVEN WHOLE INFANT SPLEENS INTRAPERITONEALLY

Experiment	Control	Experimental			
		1 spleen	2-3 spleens	4 spleens	8 spleens
A	0/5	0/5		3/5	2/5
B	0/9			0/4	0/3
C	0/7		4/5	4/14	
D	0/7			0/6	1/6
E	0/9			4/16	
F	0/12			7/16	
G	0/5			6/9	
Total	0/54	0/5	4/5	24/70	3/14

A-G carried out in a period of about eighteen months there was a significant survival of animals that had had four spleens of infant mice inserted under Nembutal anaesthesia in the peritoneal cavity immediately after X-irradiation. There is a considerable variability of the results between individual experiments and the results as a whole are not as striking as Jacobson's. He claims that the MLD for C₃H mice is raised from about 550 r to 1025 r. The quantitative differences between laboratories may be attributable to differences in strain of mice, and within laboratories to technique.

Having qualitatively confirmed Jacobson's results, we were faced with the problem: Is this effect due to the spleen as an organ, to its cellular content or to a chemical hormone?

The spleen as an organ.—In animals which survived the thirty-day observation period and died subsequently, it was noted at autopsy that one or more of the implanted spleens had "taken" and appeared as accessory spleens. If the survival of the animal were due to the "take", by increasing the percentage of "takes" one should be able to improve the rate of survival. An attempt was made to increase the "takes" by preliminary splenectomy a week or so before irradiation. This did not appear to affect the subsequent outcome. (Experiment E, 4 survivors out of 16 animals.)

Protective effects of implants of splenic tissue.—Moreover, if an integrated action of the whole organ were to produce the effect, the spleen ground in a mortar and injected as a mush intraperitoneally should be inactive. In fact, when four infant spleens were so ground up with physiological saline and injected, a positive result was obtained: Table II (Experiment I—3 survivors out of 13 animals).

TABLE II.—SURVIVAL OF MICE (950 r) GIVEN TISSUE-MUSH

Experiment	Control	Experimental			
		Mush of infant mouse spleen		Mush of adult mouse marrow	
		I.P.	I.V.	I.P.	I.V.
I	0/9	3/13			
G	0/5	0/4	3/5		
H	0/13	0/3	6/6	0/5	2/5
Total	0/27	3/20	9/11	0/5	2/5

These results are qualitatively similar to those of Cole *et al.* (1952) from San Francisco. Later experiments in which the tissue mush was injected intravenously have given superior results to those of the intraperitoneal route (Experiments G and H).

The spleen as a source of essential cells.—This positive result with splenic mush could be explained by the transference of cells undamaged by the grinding process to the recipient and their continued function within the new host as seeding material from which the recipient regenerates its destroyed tissue. Alternatively some chemical agent could be transferred in the solid or liquid phase. No active agent has so far been detected in the liquid phase. The supernatant saline after centrifugation at 3,000 revs. for twenty minutes, has failed to protect 11 mice.

This negative result by no means rules out the existence of a humoral factor, which, for instance, may not be water soluble. It was thought that another approach might be through heterospecific material. If intact cells had to survive and act as seeds, cells from an animal other than the mouse would be ineffective. On the other hand provided that donor animals' tissues contained the hypothetical hormone in the same concentration, an equivalent weight of heterospecific material should give similar positive results to homologous spleen. It should be noted that Lorenz and his colleagues (1952) at Bethesda have just claimed successes in mice with guinea-pig material—bone-marrow—into mice. However, our results with heterologous tissue, both spleen and bone-marrow, so far have been negative. Table III shows that spleens from infant rabbits and guinea-pigs and bone-marrow from infant guinea-pigs have failed to save any of our mice.

TABLE III.—SURVIVAL OF MICE (950 r) GIVEN HETEROLOGOUS MATERIAL

Experiment	Control	Experimental		
		Rabbit spleen	Guinea-pig spleen or marrow	
		I.P.	I.P.	I.V.
B	0/9	0/14	0/4	
J	0/5		0/5	
K	0/5			0/10

Protective effects of implants of splenic tissue.—From this we conclude that we have no evidence as yet for a humoral factor or alternatively that a chemical agent in rabbit or guinea-pig material is in too low a concentration to be detected by our method.

REFERENCES

- COLE, L. J., FISHLER, M. C., ELLIS, M. E., and BOND, V. P. (1952) *Proc. Soc. exp. Biol., N. Y.*, **80**, 12.
 JACOBSON, L. O., MARKS, E. K., ROBSON, M. J., GASTON, E., and ZIRKLE, R. E. (1949) *J. Lab. clin. Med.*, **34**, 1538.
 —, SIMMONS, E. L., MARKS, E. K., GASTON, E., ROBSON, M. J., and ELDREDGE, J. H. (1951) *J. Lab. clin. Med.*, **37**, 683.
 LORENZ, E., CONGDON, C., and UPHOFF, D. (1952) *Radiology*, **58**, 863.
 MOLE, R. H. (1950) Personal communication.

Section of Pathology

President—Professor G. PAYLING WRIGHT, D.M., F.R.C.P.

[November 18, 1952]

SYMPOSIUM ON THE BASIS OF ALLERGIC REACTIONS

Dr. W. N. Goldsmith: Dermatologists recognize *three* main types of reaction of the skin to tests with allergens: (1) Whealing; (2) Papular; (3) Eczematous. The two last are both delayed reactions, but one, the papular or tuberculin type, is dermal, whereas the other, the eczematous, is epidermal. Even though the basic mechanism of these two allergic reactions may be closely related or identical, and though they may co-exist, it is important to remember that they can occur quite separately, and wrong conclusions can be drawn by failing to discriminate between them. As far as possible one ought to avoid speaking of sensitization of the skin and refer specifically to sensitization of the epidermis, dermis, or of the whole skin. I am going to devote my remarks to the third type.

EPIDERMAL ECZEMATOUS SENSITIZATION

Nature of reaction.—In the state of sensitivity characterized by the delayed reaction as opposed to the anaphylactic state, Rich (1946-47) says that cells of even an avascular tissue, e.g. cornea, or indeed cells washed and isolated in tissue culture, are killed by contact with a specific antigen.

That eczematous reactivity is primarily and chiefly associated with epidermal cells is established by many observations, both histological and clinical, and even in the case of certain "endogenous" allergens, such as drugs. Thus in a case of "fixed eruption" due to phenazone, Nägeli *et al.* (1930) demonstrated, by placing Thiersch slices of reactive areas in a solution of the drug, that destructive changes occurred primarily and mainly in the prickle cells. Extraneous inflammatory cells were absent. If any adherent fragments of dermis reacted, too, it was always later.

The appropriate test is the patch test, and it is quite an uncanny thing to see a piece, for instance, of pure, clean, dry, copper foil, laid on the outside of intact skin, producing a blistering eruption, and such a patch test can be strongly positive when the same allergen introduced intracutaneously will produce no reaction. On the other hand, Rokstad (1946) described two types of reaction to patch tests in different individuals supersensitive to the same substance. In one group there was pronounced vesiculation, but only slight hyperæmia and infiltration. In the others, hyperæmia and infiltration predominated. Correspondingly, some subjects of clinical allergic eczema react relatively weakly to patch tests and strongly to intracutaneous injection, but in most the converse is found. According to Haxthausen (1949), in most cases of clinical eczema, but not all, the corium takes *some* part specifically in the reaction, for intracutaneous injection of the specific allergen generally, but not always, induces a characteristic late papular reaction of the tuberculin type. Its chronological course points to a close relation to the eczematous reaction, both generally requiring one to two days to develop.

Rokstad (1946), working with turpentine, demonstrated differences between the primary irritant effects and the allergic eczematous reaction, and showed that the toxic effect of stronger concentrations inhibited the eczematous response.

Allergens.—Allergens may consist of the simplest chemicals, even elements, e.g. nickel and copper, but, in order to sensitize, simple chemicals probably have to link with proteins to form complete antigens, and it is striking that many sensitizing substances have a marked affinity for proteins, e.g. mercurial and chromic compounds, formalin, dinitrochlorobenzene, and paraphenylenediamine. Haxthausen (1940) was able to sensitize human subjects to dinitrochlorobenzene by intramuscular injection, if this was mixed with horse serum or the patient's own serum, but not with the pure substance

in the same dose and concentration. The formation of complex antigens may be considered proved in several instances, and highly probable in others, though many allergens cannot be shown to have any affinity for proteins.

Eczematous sensitivity is more highly specific than urticarial, and a further difference is that repeated applications of the allergen do not lead to a fall in reactivity, but rather the reverse.

An important antigen can be derived from skin itself. Since Whitfield's work (1921), it has been widely recognized that in an eczematous patient the epidermis can become sensitized to contact with the exudate from a damaged area. Much clinical experience suggests that secondary and recurrent patches of eczema are caused by general sensitization to *absorbed* skin antigen. This is difficult to prove. We know, of course, from surgical experience in grafting that *homogenous* epidermis *always* acts as antigen.

Mechanism of sensitization.—Hitherto the most reliable experimental method has been the primary application of the substance to the skin itself, perhaps because it there acts on tissue proteins for a longer period and at a higher concentration than if introduced elsewhere. But many experiments have shown that hypersensitivity limited to the skin *can* be produced by primary injection into some other part of the body. Thus Landsteiner and Chase in 1939 showed that intraperitoneal injection of picryl chloride, mixed with a suspension of killed tubercle bacilli, induced hypersensitivity to picryl chloride limited to the skin (epidermis).

Even when the primary application is made to the *skin*, does the process of sensitization take place *in situ*? To answer this, Landsteiner and Chase (1940) made skin islands about 35 mm. in diameter in guinea-pigs by excising a ring of skin around them. In some, the incisions were relatively superficial; in others they were deep enough to include the panniculus carnosus. When poison ivy extract was painted on to an island, if the moat was superficial, hypersensitivity appeared on the island and outside it as well; if the moat was deep, no hypersensitivity developed at all, even on the island. If the extract was painted on the skin *outside* a deeply moated island, hypersensitivity developed both outside and on the island. These findings indicate that the antibody production does not take place locally in the skin, but centrally, and that the antibodies are transported to the skin by the bloodstream. Presumably the absorption of enough complex antigen depends on intact lymphatics and on the exposure of an adequate amount of tissue to the allergen.

Seeberg (1951) sensitized guinea-pigs by one exposure to dinitrochlorobenzene by the following routes: epidermal, intracutaneous, subcutaneous and into an inguinal lymph gland. The subcutaneous route was less successful than the other three, but the lymph-gland route was equally successful with the epidermal and the intracutaneous routes.

If antibody production is central, there are some difficulties with regard to localization of sensitivity. In most cases of allergic eczema, it is true, all areas of the skin react positively to patch-tests, though in varying degrees. In some cases, however, a positive patch test is found only in or near the eczematous eruption. Haxthausen (1949) seeks to explain this by the existence of greater "unspecific lability" of eczematous skin and adjacent areas. In human subjects sensitized with dinitrochlorobenzene, he found that generally the positive reaction appeared first in the area of primary application. This, too, he attributed to unspecific lability set up by the irritant action of the primary application. After a few days all other parts of the skin reacted, and it was not possible to demonstrate any gradual spreading from the primary area to distant regions. But in the following case observed by me, such spreading from the primary area *did* seem to happen (Cavendish, 1940). It was an instance of primary sensitization and spontaneous flare-up *in situ*:

A chemistry research worker presented himself with an unusual, severe, dusky-red, bullous eruption. Patch tests with suspected chemicals were negative except for 9-bromo-fluorene, which gave a mild reaction. As this might have been a simple irritant effect, it was tested on three controls, none of whom was likely to have come in contact with it before. The patch tests consisted of laying a small spot of the powder on the surface of the skin for twenty-four hours, and then cleaning it off. In the first control, nothing happened at all. In the second control, after eight days, a few temporary blisters occurred *at the site of the patch test*. The third control was more exciting. When the patch test was removed after twenty-four hours, there was only faint erythema, which quickly vanished. After thirteen days, *at the site of the patch test*, redness and blisters developed and spread *contiguously* over a wide area in a form closely imitating that of the original patient. Now, if the antibodies are formed centrally, why does the flare-up occur at the site of the patch test? Non-specific lability seems a strained explanation. Why in that case did it not begin with preference where the plaster was ripped off? Possibly the explanation in this case is the simple one that there was still a greater concentration of allergen there than at any other part of the skin. But why the extension by contiguity? You may feel that it is quite natural for inflammation to spread. But is it? A positive reaction to a patch test or an allergic reaction to the application of a piece of Elastoplast, for instance, or the non-allergic patch of inflammation produced by a Kromayer lamp, generally remains sharply limited to the original area of application. Moreover, the eruption in this control was not banal, but resembled that of the original case. If antibody production in the skin itself can occur, then the following hypothesis is suggested:

The portion of test substance absorbed into the skin during the twenty-four hours of application diffused outward during the subsequent latent period, initiating the sensitizing process in widening

zones
and the
by the

If, on
the lat
any c

The
sensit
the ori

If the
primary
with d

tions s
reduced

This ca
this an
with ep

Perh
Even

Pass
been ne
to critic
into a t
applic

To d
the fac
pairs of
sensitiz

to the m
epiderm

ment, a
indicate

any rate
dinitro
after a

When
cytes. T

In 1947
periton

that if
sensitiz

a wide
epiderm

improb
of sens

presen
clearly

and is
Haxtha

not very
transpl

epiderm
reactio

of urtic
into the

no firm
the ly
cells: t
Are the
Dit
probab

The
cann
that p

zones, one after the other. When the necessary thirteen days were up, the site of application reacted, and then successive zones followed suit at the same rate as the antigen had originally diffused, each by the same mechanism and after the same respective latent period.

If, on the other hand, antibodies are only produced centrally and circulated to the skin, then, after the latent period, any flare-up should take place simultaneously wherever there is any antigen. In any case, we do not understand the sudden change from latency to explosion.

The Shwartzman phenomenon is also strongly in favour of the skin being itself the site of the sensitization process. Here the localization cannot possibly be due to there being more allergen at the original site, because the reaction is evoked by intravenous injection of fresh allergen.

If the process of sensitization is a local one, it should not depend on the extent of skin treated primarily by the antigen, but only on its concentration. Indeed Miescher (1941), by painting guinea-pigs with different strengths of alcoholic solution of dinitrochlorbenzene, did show that higher concentrations sensitized more successfully, even though acting on smaller areas. But Haxthausen (1949) reduced this to an extreme by pricking the skin with a pin dipped in melted dinitrochlorbenzene. This caused a tiny red papule, but never any local or universal hypersensitiveness. He considered this an argument against a local mechanism. But here I feel that the amount coming in contact with epidermal cells would be subliminal.

Perhaps we are justified in concluding that both local and central mechanisms exist.

Even endogenous antigens (drugs) can sensitize epidermis in sharply demarcated patches.

Passive transmission.—Most attempts by modification of the Prausnitz-Küstner technique have been negative, whether serum has been used or blister fluid: and some of the positive reports are open to criticism because the reaction elicited was urticarial. But Urbach (1944) injected intracutaneously into a test subject the contents of a blister from a case of primula eczema, and over this site subsequently applied a primula leaf. This evoked a typical eczematous reaction.

To demonstrate the existence of circulating eczematous antibodies, Haxthausen (1943) made use of the fact that successful skin grafts can be made from one uniovular twin to the other. Using two pairs of twins, he sensitized one of each pair by epidermal application of dinitrochlorbenzene. When sensitization had been established, a piece of untreated skin from the sensitized twin was transplanted to the non-sensitized twin, and vice versa. The grafts healed well. Three weeks after the transplantation, epidermal tests revealed that the sensitive transplant had lost its sensitiveness in the normal environment, and that the normal transplant had acquired sensitiveness in the sensitized environment. This indicates that the state of eczematous hypersensitiveness is due to the presence of circulating, or at any rate diffusible antibodies. That they do circulate was further clinched by sensitizing guinea-pigs to dinitrochlorbenzene and then uniting them with untreated animals by parabiosis. In most cases, after a few days, the non-sensitized animals gave a positive epidermal reaction.

Whereas sensitiveness cannot be transferred by means of serum, it has been transmitted by lymphocytes. This was first shown rather inconclusively in 1942 by Landsteiner and Chase with picryl chloride. In 1947, Haxthausen transmitted sensitiveness to dinitrochlorbenzene and to Dioxanthogen by intraperitoneal injection of lymphocytes from the *thymus* of sensitized animals, but it is important to note that if he injected lymphocytes *intracutaneously* he was unable to transfer sensitivity either from sensitized animals or from human cases of allergic eczema from various causes. This brings us to a wide gap in our knowledge, namely *how do the lymphocytes transfer the antibodies to the avascular epidermis?* One would think that it could only be through the medium of the plasma, for it is most improbable that there is any invasion of the epidermis by lymphocytes during the symptomless period of sensitization. One only sees such invasion in severe inflammations or lymphomas, and their presence in the epidermis is certainly not required for the reaction itself, as Nägeli's experiments have clearly shown. It has been suggested that if the antibody has strong affinity for the cells of the skin, and is produced slowly in limited amount, the concentration in the blood would remain low. But Haxthausen's transplant experiment showed that the antibody to dinitrochlorbenzene at any rate was *not* very firmly held by epidermal cells (here, however, there is a little discrepancy with Nägeli's *auto-transplants* in phenazone fixed eruption, which *did* indicate considerable fixity of antibodies to certain epidermal cells). The absence of antibodies from the serum, as well as the long latent period of the test reaction, have been attributed to the antibodies being located deeply in the cells (in contrast to those of urticaria, which seem to be regarded as standing recklessly on deck and being washed overboard into the blood stream). But located deeply in which cells? We have just seen that they may retain no firm anchorage to epidermal cells when transplanted, and if they are stowed deep in the hold of the lymphocytes it is still more difficult to understand how they are trans-shipped to the epidermal cells: and why does not fresh allergen, especially if introduced internally, disrupt the lymphocytes? Are the antibodies present there only in some precursor form?

Dinitrochlorbenzene sensitiveness in female guinea-pigs is not transmitted to the offspring, so probably the antibody is a high molecular protein.

The ultimate mechanism, i.e. the consequence of the allergen-antibody encounter.—*Histamine* cannot reproduce the eczematous type of reaction. Neither in eczema caused by chemicals nor in that produced by sensitization to ultraviolet rays can histamine-release be shown to be instrumental,

and antihistaminic drugs, as such, neither prevent nor cure it. Possibly the ultimate mechanism is of the kind worked out by Peters (1945), in which there is release of a tissue protease. But leucotaxis, if it occurs, is only a secondary phenomenon. The reaction itself is seen histologically as an oedema in and between the prickle-cells, which burst. Both Rich and Nägeli have shown clearly that this is independent of the presence of blood vessels or extraneous inflammatory cells.

Are the clinical differences between the characteristic effects of certain allergens referable entirely to the selection of cells by antibodies, or may it be that the ultimate mechanism does differ to some extent with different allergen-antibody encounters?

ACTH and cortisone.—In contrast to antihistaminic drugs, cortisone is more inhibitive in the delayed than in the immediate type of allergic reaction, and in epidermal more than in dermal responses. Cruickshank (1952) has found that there is slight inhibition of reactions to patch tests. Topical application to the skin is ineffective.

REFERENCES

- CAVENDISH, A. (1940) *Brit. J. Derm.*, **52**, 155.
 CRUICKSHANK, C. N. D. (1952) Personal communication.
 HAXTHAUSEN, H. (1940) *Acta derm.-venereol., Stockh.*, **21**, 1.
 — (1943) *Acta derm.-venereol., Stockh.*, **23**, 438.
 — (1947) *Acta derm.-venereol., Stockh.*, **27**, 275.
 — (1949) Chapter on "Allergy in Diseases of the Skin" in Kallós, P. (1949) *Progress in Allergy*. Basle, 2, 167.
 LANDSTEINER, K., and CHASE, M. W. (1939) *J. exp. Med.*, **69**, 767.
 — (1940) *J. exp. Med.*, **71**, 237.
 — (1942) *Proc. Soc. exp. Biol., N.Y.*, **49**, 688.
 MIESCHER, G. (1941) *Schweiz. med. Wschr.*, **22**, 1360.
 NÄGELI, O., DE QUERVAIN, F., and STALDER, W. (1930) *Klin. Wschr.*, **9**, 924.
 PETERS, R. A. (1945) *Brit. med. Bull.*, **3**, 81 (cit. Pickering, 1952).
 PICKERING, G. W. (1952) *Brit. med. J.*, **i**, 1207.
 RICH, A. R. (1946-47) *The Harvey Lectures*. Philadelphia: The Science Press.
 ROKSTAD, J. (1946) *Skin Reactions Caused by Fractions of Oil of Turpentine and Hexanitrodiphenylamine*. Oslo.
 SEEBERG, G. (1951) *Acta derm.-venereol., Stockh.*, **31**, 592.
 URBACH, E. (1944) *Allergy*. London.
 WHITFIELD, A. (1921) *Lancet*, **ii**, 61, 122, 168.

Dr. W. Feldberg: *Recent experiments about histamine and allergic reactions.*—My contribution to this symposium is concerned with skin histamine and its release under various conditions. In the past, methods for studying histamine release from tissues have been limited because we had few means by which we could produce an effective release without damaging the tissue. The position has changed, particularly through the work of MacIntosh and Paton (1949), and we have now at our disposal a variety of substances, some simple amines, some chemically more complicated substances, which when injected into an animal or into the artery of a perfused organ release histamine without producing visible tissue damage: the so-called histamine liberators. The one used in the present experiments is compound 48/80, a condensation product of p-methoxyphenethyl-methylamine.

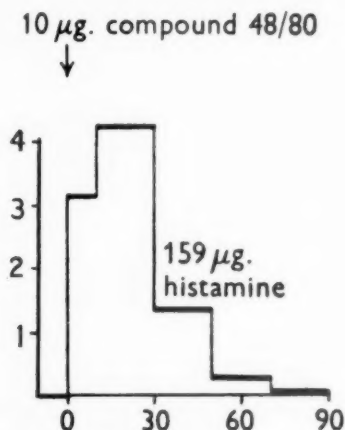


FIG. 1.—Histamine output from perfused flap of cat's skin by 10 µg. compound 48/80. Ordinates: histamine µg./min.; abscissa, time in minutes after arterial injection of 48/80. Total histamine output 159 µg. (From Feldberg and Paton, *J. Physiol.*, 1951.)

Paton and I (1951) perfused a flap of cat's skin with Tyrode's solution from the artery (the saphenous) and then injected a few μ g. of 48/80 into the artery, with the result that histamine appeared in the venous effluent. Fig. 1 illustrates this release of histamine from a perfused skin flap by an arterial injection of 10 μ g. compound 48/80.

When 48/80 is injected into the whole animal, the histamine released in the skin causes increased permeability of the skin capillaries at the site of its liberation, and if the consequent fluid exudation is sufficient, oedema results. If not, the increased capillary permeability can still be detected by injection of a colloidal dye. Miles and Miles (1952) used pontamine sky blue for this purpose. Skin areas in which the permeability of the capillaries is increased become quickly blue.

Miles and I (1953) injected 48/80 intravenously into guinea-pigs with circulating pontamine blue. The skin did not blue at once all over the body. Blueing started, and became intense within a few minutes, in the eyelids, around the mouth, at the base of the ear, in the submental region; during the following minutes the blueing spread all over the head and neck region and was intense around the areolar area of the nipples. This is illustrated in Fig. 2. There was also some deep blueing in the perineum; but the trunk and hind legs were only faintly stained and the staining was often patchy.

If the degree of blueing is, as we assume, dependent on the state of permeability of the capillaries, then these findings would represent a regional pattern of increased permeability of the skin capillaries after 48/80; and the question arises what is the cause?

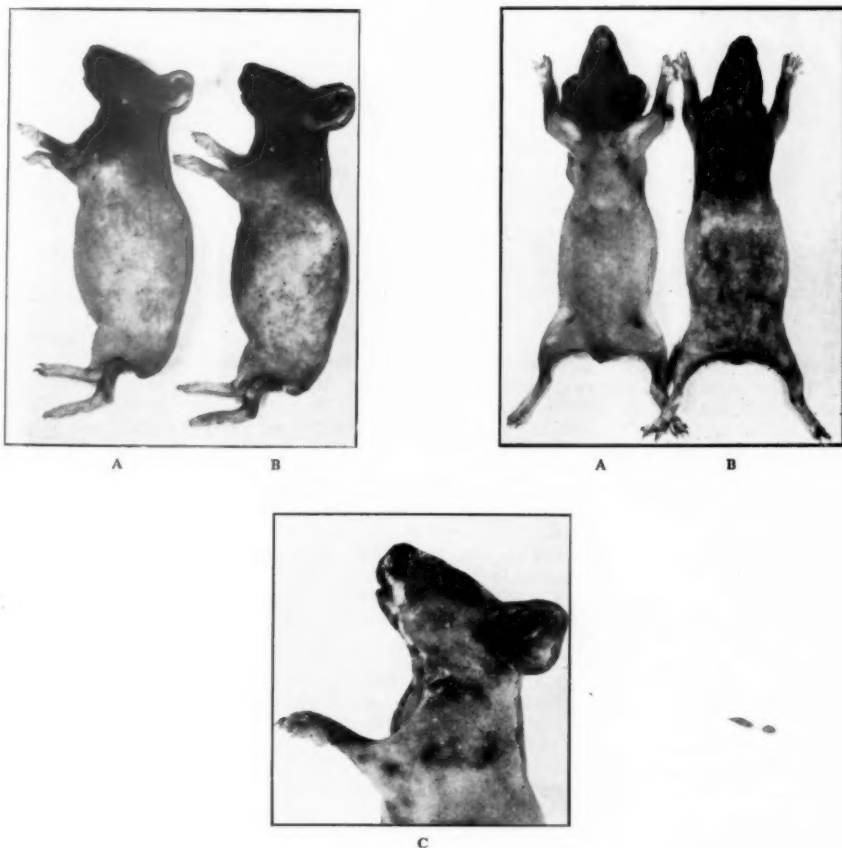


FIG. 2.—Blueing of the skin after intravenous injection of 48/80 into three guinea-pigs with pontamine blue in their circulation. Animals A and B were killed after full blueing had developed, and depilated. Guinea-pig C was killed before the blueing was complete to show the early blueing round the lips, nose, eyes and ears. The depilation of this animal is faulty; the white areas round the mouth and along the base of the jaw are remnants of hair. (From Feldberg and Miles, *J. Physiol.*, 1953.)

Miles and I determined the histamine content in various skin regions and found that the regional pattern of blueing was, with one exception (the distal parts of the legs), directly related to the histamine content of the skin. The regional variations of histamine content of the skin of the guinea-pig are seen from Fig. 3. Miles has recently shown that in guinea-pigs sensitized with various antigens, the simultaneous injection of antigen and pontamine sky blue produces blueing which extends to the feet as well, so that in this allergic phenomenon the agreement between skin histamine content and increased capillary permeability is even better than after 48/80.

Similar regional patterns concerning histamine content and proneness to increased permeability of the skin capillaries were found to exist in other species. For instance, Paton and Schachter (1951) describe the oedema which occurs in dogs after a subcutaneous injection of 48/80. There was facial swelling "particularly marked in the bristle area near the mouth, the eyelids and the pinna of the ears. These areas also showed considerable erythema. Oedema and erythema of other regions was not observed except for the nipple area in one animal". Miles and I found that the five skin regions with the highest histamine content in dogs were again the bristle-bearing area, the eyelids, the ears, the lips and the areola of nipples; i.e. those regions which became oedematous in Paton and Schachter's dogs.

In one more species, the rat, Talesnik and I found that an intraperitoneal injection of 48/80 leads to signs of itching—as it does in guinea-pigs and dogs—and to oedema of a characteristic distribution, namely in the face, the ear, the back of the head, the perineal region and the paws, sometimes spreading over the whole leg. Again, these skin regions yield higher histamine values on extraction than the abdominal skin. Although there is a direct relation in several species between skin histamine and proneness to increased capillary permeability, other factors must not be forgotten. For instance, the mechanical factor; the looseness

of a tissue will determine the degree of oedema in those areas in which increased permeability occurs.

One further point must be mentioned. Apart from regional differences in skin histamine, there are great species differences in the histamine content of the skin. The meaning of these differences is not clear, but as far as the evidence is available, the regional differences seem to occur, at least to a certain extent, whether the general level of skin histamine of a species is high or low. The question naturally arises whether similar regional differences in skin histamine exist in the human, and, if so, whether they can be related to regional differences of allergic and other dermatological manifestations.

To return to the experiments on rats. Talesnik and I (1953) succeeded in greatly reducing and practically depleting the histamine in the skin and skeletal muscle of rats by repeated intraperitoneal injections of 48/80 in increasing dosage. A dose of 48/80 which on first injection causes severe oedema of the characteristic distribution becomes ineffective after several injections; but at this stage the rats respond again to larger doses of 48/80 until they become also ineffective on repeated injections. When the rats are then killed, the skin and muscle histamine is found to be low. This is illustrated in Fig. 4. A. N. Smith and I tried to repeat these findings in guinea-pigs and mice, but succeeded in reducing the skin histamine to a relatively small extent only; in cats, Smith (1953) was able, however, to reduce the skin histamine by 48/80 as much as in rats. Once the skin histamine is "depleted" it takes a long time until it is restored (Fig. 3). This finding gave us the opportunity to study in rats with very low histamine content of the skin, skin reactions closely related to allergic phenomena.

Rats are hypersensitive to egg white, as shown by Selye (1937). That is, its first intraperitoneal injection in the non-sensitized animal leads to oedema in the face and paws; in fact the distribution of the oedema is the same as that seen after 48/80. We were interested in this oedema, because of the question whether it was an effect of histamine released by the egg white in the skin and acting locally at the site of its liberation. The answer to this question would be simple if intravenous injections of histamine would reproduce the effect, but they do not. On the other hand, the oedema is prevented by antihistamine drugs and, further, Schachter and Talesnik (1952) were able to show that, injected into rats, egg white released histamine. The question then was: what would be the effect of egg white in rats in which the skin histamine had been greatly reduced or practically depleted? Talesnik and I found that in such rats egg white no longer produced oedema. The rats had, so to speak, become resistant to egg white because there was no longer sufficient histamine available in the skin to be released by it and to cause the increased capillary permeability at the site of release.

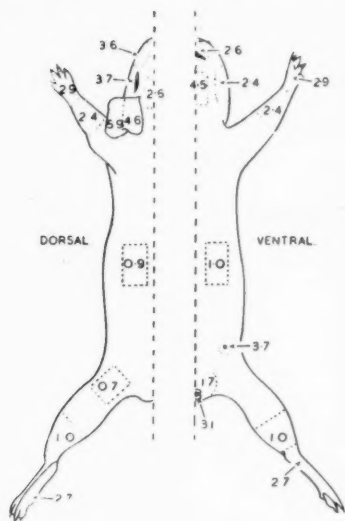


FIG. 3.—Distribution of histamine in various regions of guinea-pig's skin. The abdominal skin taken as unity; its histamine content varied between 2.1 and 4.0 $\mu\text{g./g.}$ (mean 3.2 $\mu\text{g./g.}$). (From Feldberg and Miles, *J. Physiol.*, 1953.)

When these results were communicated to the Physiological Society, Sir Henry Dale suggested that Talesnik and I also test the effect of light in photosensitized rats after treatment with 48/80. Professor C. Rimington kindly provided us with some purified hæmatoporphyrin. When normal rats were exposed to the light from a carbon lamp, twenty hours after an intraperitoneal injection of hæmatoporphyrin, they became restless, started to scratch violently and then one group of rats became listless and weak and was sitting in the cage with ruffled fur and intense cyanosis; some rats died. The other group of rats developed oedema in the face, head, ears and in the paws.

On the other hand, rats treated first with 48/80 and then injected with hæmatoporphyrin showed a definite resistance to light. Apart from some scratching during the exposure to light, some of these rats showed no further signs; the other rats became slightly swollen in the ears but all other effects seen in the control rats were absent and none died. So at least two kinds of skin phenomena closely related to allergic reactions can be more or less prevented in rats in which the skin histamine has been greatly reduced.

In the oedema produced in rats by 48/80, egg white or light, we encounter a phenomenon which is due to histamine but which cannot be reproduced by intravenous histamine injections, because they do not imitate the local effect of histamine at the site of its release.

On the other hand, a histamine-like effect does not need to be due to histamine. An allergic contraction of a smooth muscle, although reproducible by histamine, can well be the result of another pharmacologically active substance released by the antigen-antibody reaction or the "allergen". Recently, Humphrey and Jaques (1952) reported that the antigen-antibody reaction releases from the rabbit's platelets not only histamine but another pharmacologically potent smooth-muscle-contracting

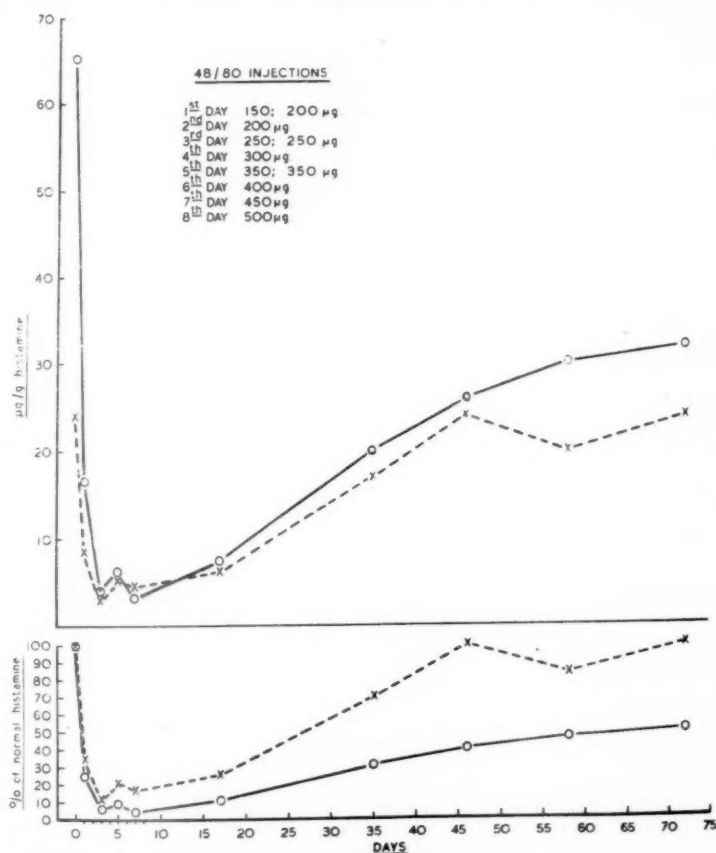


FIG. 4.—Effect of intraperitoneal injections of 48/80 on histamine content of rat's skin from abdomen (x---x) and feet (o---o). Upper tracings histamine content expressed in µg./g. skin; lower tracings in percentages of normal values. Eight days' treatment with increasing doses of 48/80 as indicated. (From Feldberg and Talesnik, *J. Physiol.*, 1953.)

substance, 5-hydroxytryptamine (serotonin). We do not yet know if this amine is released only from platelets or from the tissues as well, and if it plays a role in the symptomatology of allergic phenomena.

REFERENCES

- FELDBERG, W., and MILES, A. A. (1953) *J. Physiol.* (In press.)
 —, and PATON, W. D. M. (1951) *J. Physiol.*, **114**, 490.
 —, and TALESNIK, J. (1953) *J. Physiol.* (In press.)
 HUMPHREY, J., and JAKES, R. (1953) Proceedings of the meeting of the Physiological Society, December 1952. *J. Physiol.*
 MACINTOSH, F. C., and PATON, W. D. M. (1949) *J. Physiol.*, **109**, 190.
 MILES, A. A., and MILES, E. M. (1952) *J. Physiol.*, **118**, 228.
 PATON, W. D. M., and SCHACHTER, M. (1951) *Brit. J. Pharmacol.*, **6**, 509.
 SCHACHTER, M., and TALESNIK, J. (1952) *J. Physiol.*, **118**, 258.
 SELYE, H. (1937) *Endocrinology*, **21**, 169.
 SMITH, A. N. (1953) Personal communication.

Professor J. R. Marrack: *The antibodies involved in allergic reactions.*—The Prausnitz-Küstner reaction shows that the serum of allergic subjects contains a substance that reacts specifically with the corresponding allergen. This substance, called a reagin, behaves therefore as an antibody, but it has certain peculiarities. The reagin seems to be distinct from the ordinary precipitable antibody; in most cases the serum of allergic patients does not form a precipitate with the corresponding allergen. Sensitizing substances comparable to reagin may appear in the serum of normal persons after injections of horse serum, but the amount of reagin, as measured by the minimum amount that will give a P.K. reaction, does not run parallel to the amount of precipitable antibody (Tuft and Ramsdell, 1929).

Of recent years the investigations on erythroblastosis foetalis have drawn attention to incomplete antibodies and there is a tendency to imagine that "incompleteness" may account for any peculiarities of antibodies. An antibody is said to be incomplete when it will not form a precipitate with, or agglutinate, the corresponding antigen. I deprecate the use of the term "univalent"; for, though there is now good evidence that the precipitating antibodies are bivalent, there is no evidence that incomplete antibodies are univalent.

The concept of incomplete antibodies started in 1935 when Heidelberger and Kendall found that when 7.6 mg. of the antigen, ovalbumin, were added, in one instalment, to 5 ml. rabbit antiserum, 91 mg. of antibody protein were precipitated from the antiserum and they also found that no antigen or antibody could be detected in the supernatant fluid. If, however, ovalbumin was added in small instalments, until no further precipitate formed, only 71 mg. of protein were precipitated. Heidelberger and Kendall inferred that the 5 ml. of antiserum contained $91 - 71 = 20$ mg. of antibody that would not, by itself, form a precipitate with antigen, but would combine with vacant sites on antigen molecules precipitated by ordinary antibody molecules. When small instalments of antigen were added they combined preferentially with the precipitable (complete) antibody. They found that this 20 mg. left unprecipitated was carried down with the precipitate formed by a further lot of antiserum to which a suitable amount of ovalbumin was added in one instalment.

There is no reason to suppose that the formation of incomplete antibodies is an abnormal occurrence. Most of the antibody formed by dogs in response to injections of a protein such as ovalbumin is incomplete and rabbits form varying amounts of incomplete antibodies. It is difficult to decide whether the skin-sensitizing antibody formed, for example, by a rabbit immunized with ovalbumin is actually contained in the incomplete fraction as Sherman *et al.* (1950) have claimed. In response to injections of ovalbumin rabbits may form considerable amounts of antibodies to other proteins, which are contained as impurities in the sample of ovalbumin used (Munoz and Becker, 1950). When the greater part or all of the antibody against ovalbumin has been precipitated, these other antibodies are left in the supernatant fluid; if the allergen is one of these impurities the amount of the serum required to sensitize the skin passively will be unaffected. Sherman *et al.* (1950) did not exclude this possibility; and Orlans (1952, unpublished) found that the serum of an egg-sensitive patient formed a precipitate with an impurity of ovalbumin. Similarly, Bukantz *et al.* (1949) found evidence of an incomplete antibody in the serum of patients who had had a course of injections of ragweed pollen extract; this suggests that the blocking antibody was also an incomplete antibody. But the incomplete antibody detected may well have not been antibody against the allergen, but against some other constituent of the pollen extract. Becker and Munoz (1949) have shown by Oudin's (1947) method that antisera against ragweed pollen contain antibodies against several antigens.

Unless the allergen is isolated in a fairly pure state it is difficult to decide whether any antibody, complete or incomplete, is actually antibody against the actual allergen. Orlans, Rubinstein and Marrack (1953) demonstrated by Boyden's (1951) method antibodies in the serum of hay-fever patients who had been treated with injections of pollen extract. But we could not infer that these were the blocking antibodies.

The reagins may well be incomplete antibodies, but incompleteness is not the feature that distinguishes them from other antibodies. One feature that appears abnormal is that they become firmly attached where they are injected and may remain for several days, whereas other antibodies, including the blocking antibodies, diffuse away. A peculiarity of allergic persons is not so much that they form

reagins, as that they may form reagins after absorption in small amounts of substances that are poor antigens, and may go on forming these reagins long after contact with the antigens has ceased. Normal persons will form reagins after injection of good antigens, such as horse serum (Tuft and Ramsdell, 1929); but these reagins disappear from the serum in about two weeks.

REFERENCES

- BECKER, L., and MUNOZ, L. (1949) *Proc. Soc. exp. Biol., N.Y.*, **72**, 287.
 BOYDEN, S. V. (1951) *J. exp. Med.*, **93**, 107.
 BUKANTZ, S. C., JOHNSTON, M. C., and HAMPTON, S. (1949) *J. Allergy*, **20**, 1.
 HEIDELBERGER, M., and KENDALL, F. E. (1935) *J. exp. Med.*, **62**, 697.
 MUNOZ, L., and BECKER, L. (1950) *J. Immunol.*, **65**, 47.
 ORLAND, E. S., RUBINSTEIN, L. J., and MARRACK, J. R. (1953) *Acta allerg., Kbh.* (In press).
 OUDIN, J. (1947) *Bull. Soc. Chim. biol., Paris*, **29**, 140.
 SHIRMAN, W. B., MENZEL, A. E. O., and SEEROHM, P. M. (1950) *J. exp. Med.*, **92**, 191.
 TUFT, L., and RAMSDELL, S. G. (1929) *J. Immunol.*, **16**, 411.

Dr. J. F. Ackroyd: *Purpura due to hypersensitivity to Sedormid (Allyl-isopropyl-acetyl-carbamide).*—Purpura due to Sedormid is characterized by the rapid development of thrombocytopenia and increased capillary fragility whenever the drug is taken by a sensitized individual. These changes result in extensive hemorrhages throughout the body.

The usual clinical story is that the drug has been taken over a period of days, weeks, or sometimes even years, with no untoward result and then suddenly, following a single dose, an attack of purpura has ensued. If no further Sedormid is taken recovery is rapid and is usually complete within a week. The hypersensitivity, once it has been established, persists for a long time. It is not known whether it can ever disappear entirely.

The diagnosis can be confirmed only by showing that the administration of a test dose of the drug, after recovery, gives rise to a further attack of purpura.

Action of Sedormid on the platelets.—Studies of blood clotting in the presence of Sedormid have shown that Sedormid greatly reduces clot retraction in the blood of sensitized individuals (Ackroyd, 1949a). This is due to lysis of platelets by Sedormid during coagulation (Ackroyd, 1949b).

Sedormid also causes agglutination and lysis of platelets when added to the fluid blood of sensitized patients (Ackroyd, 1949c). The lysis of platelets by Sedormid in the heparinized plasma of a sensitized patient is shown in Fig. 1.

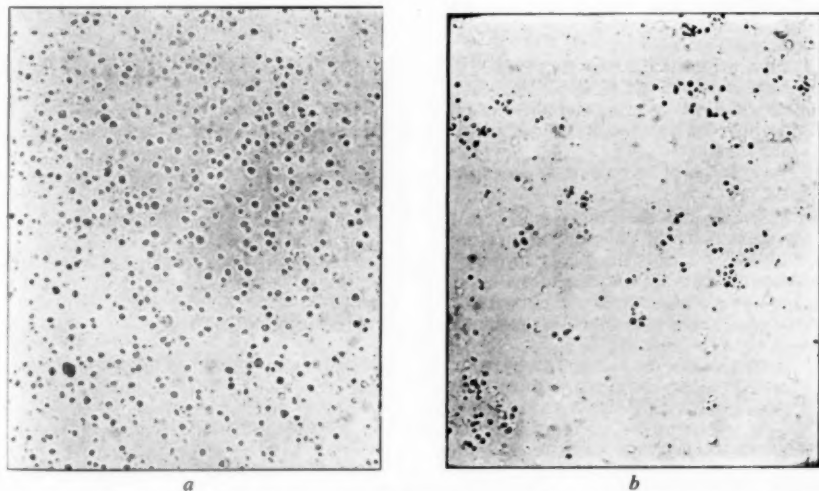


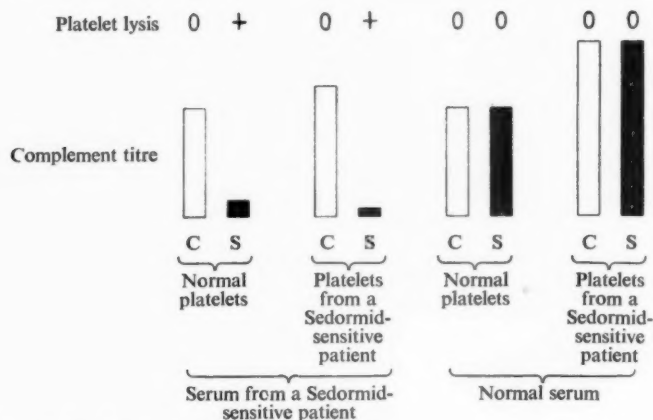
FIG. 1.—Platelet lysis by Sedormid in heparinized plasma from a Sedormid-sensitive patient. (a) Plasma + saline. No platelet agglutination or lysis. (b) Plasma + Sedormid in saline. There is considerable platelet lysis. Some platelet "ghosts" can still be seen. Most of the remaining platelets are agglutinated. (Reproduced from *Progress in Allergy*, 1952, **3**, 552.)

Platelet lysis by Sedormid involves the fixation of complement (Ackroyd, 1951).

Sedormid has no action on the blood of controls.

If platelets isolated from normal blood are suspended in normal sera and in the sera of Sedormid-sensitive patients, and the platelets of such patients are suspended in normal sera and in the sera of Sedormid-sensitive patients, and the action of Sedormid on the resulting mixtures is observed, it

will be found that Sedormid causes platelet lysis and complement fixation only in preparations containing serum from Sedormid-sensitive patients. In other words, Sedormid causes lysis of both normal platelets and those of Sedormid-sensitive patients when these are suspended in serum from sensitized patients, but the platelets of sensitized patients are not lysed by Sedormid in normal sera. These findings are shown schematically in Fig. 2. They show conclusively that the abnormality in the blood of patients who have recovered from Sedormid purpura lies in the serum and not in the platelets (Ackroyd, 1951).



C Platelet suspension in serum was diluted with saline.

S Platelet suspension in serum was diluted with a saturated solution of Sedormid in saline.

FIG. 2.—Platelet lysis and complement fixation by Sedormid in suspensions of platelets from a normal patient and a Sedormid-sensitive patient in the homologous and the heterologous serum. (Reproduced from *Progress in Allergy*, 1952, 3, 531.)

The complement-fixation reaction has been used to analyse the action of Sedormid, and it has been shown that:

- (1) Platelets are essential for complement fixation by Sedormid.
- (2) Red and white cells cannot replace platelets in this reaction.
- (3) Heating the sera of sensitized patients at 56° C. for half an hour inactivates the complement but does not destroy the lytic factor. This can be demonstrated in the heated sera after the addition of further complement.
- (4) In the absence of complement, Sedormid causes agglutination of platelets, but does not cause platelet lysis.

Action of Sedormid on the capillaries.—The application of Sedormid to the skin of sensitized patients causes the appearance of petechial hæmorrhages in the area of skin to which the patch is applied (Ackroyd, 1949a). The affected area shows neither hyperæmia nor wheal formation; which suggests that the hæmorrhages are not due to the release of histamine. The skin over the rest of the body is normal and the platelet count is unaltered. Sedormid has no effect on the skin of controls. The appearance of the skin of a sensitized patient after the application of Sedormid for forty-eight hours is shown in Fig. 3.

These investigations show that Sedormid causes platelet lysis in the blood of sensitized patients. This is presumably the cause of the thrombocytopenia in Sedormid purpura. Sedormid also causes hæmorrhages in the skin of such individuals. These appear to be independent phenomena, for platelet lysis occurs *in vitro*, and the capillary hæmorrhages produced by patch testing occur in the absence of thrombocytopenia.

The observations on platelet lysis show that four factors are concerned; platelets, Sedormid, complement, and the serum of a sensitized patient. Platelet lysis does not occur in the absence of any one of these factors, although platelet agglutination occurs in the absence of complement. No other immune lytic reaction appears to have been described in which more than three participating factors are involved, namely: antigen, antibody and complement. In the lysis of platelets by Sedormid it seems probable that the antibody is in the patient's serum. If this is so, then it suggests that a union of Sedormid with platelets may constitute the antigen, this antigen undergoing lysis in the presence of antibody and complement. This concept readily explains the agglutination of platelets, without lysis by Sedormid in the absence of complement, for in all immunological reactions characterized by agglutination and lysis, agglutination of the antigen occurs in the absence of complement, although complement is necessary for lysis.

FIG. 3. propylene. The skin (Reproduced from Ackroyd, 1949a).

As Sedormid is therefore proportional to the development of the disease.

It is clear that their blood union with causes platelet lysis and causes platelet lysis.

ACKROYD

BEDSON

Dr. R. in disease the relation

Our studies of corticosteroid doses of causal mechanism of a variety of corticosteroid 200 mg. by (1) and with the hypersensitivity grass pollen (1) 7/8 and A. treatment of the disease Long and the lesion

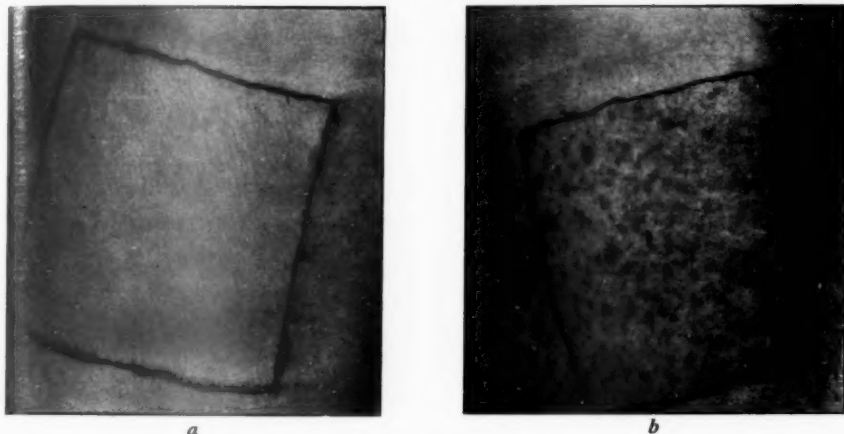


FIG. 3.—Result of patch testing a patient who had recovered from Sedormid purpura. (a) Control using propylene glycol alone. The skin in the area of the patch appears normal. (b) Sedormid in propylene glycol. The skin which has been in contact with Sedormid shows numerous closely packed petechial hemorrhages. (Reproduced from *Clin. Sci.*, 1949, 7, 285.)

As Sedormid causes, *in vitro*, lysis of the platelets of normal individuals, it would seem that this Sedormid-platelet antigen must be formed whenever Sedormid comes into contact with platelets and, therefore, that it is present in the blood stream in all patients taking the drug. That only a minute proportion of these develops purpura can best be explained on the supposition that the union of Sedormid with platelets results in a compound of extremely low antigenicity, and that only those patients whose immunity reactions are stimulated by this antigen will manufacture the antibody, and so develop thrombocytopenia.

It is clear, therefore, that patients who have recovered from Sedormid purpura probably have, in their blood stream, an anti-platelet antibody which can cause lysis of platelets rendered antigenic by union with Sedormid. Now Bedson (1922) has shown in animals that anti-platelet serum not only causes platelet lysis, but also damages the vascular endothelium. It seems reasonable, therefore, to suppose that the capillary damage in Sedormid purpura is due to the action of the antibody which causes platelet lysis, and it may tentatively be suggested that Sedormid may combine with the endothelial cells to form a further antigen which then reacts with this antibody, so causing the vascular lesion which plays such an important part in the development of purpura.

REFERENCES

- ACKROYD, J. F. (1949a) *Clin. Sci.*, 7, 249.
 — (1949b) *Clin. Sci.*, 8, 235.
 — (1949c) *Clin. Sci.*, 8, 269.
 — (1951) *Clin. Sci.*, 10, 185.
 BEDSON, S. P. (1922) *J. Path. Bact.*, 25, 94.

Dr. R. R. H. Lovell: *Cortisone and allergy.*—The discovery of the effects of cortisone and ACTH in diseases known or suspected to involve hypersensitivity has stimulated a number of enquiries into the relationship between these hormones and allergy.

Our studies in this field have so far been concerned with the more general problem of the effects of cortisone and ACTH on inflammatory reactions. We have tried to discover if therapeutically effective doses of cortisone and ACTH affect inflammatory processes generally, or only those with special causal mechanisms or types of tissue response. For this purpose we have compared the development of a variety of experimentally induced inflammations in the skin of patients before, during and after cortisone and ACTH administration. Treatment has usually been given for two weeks, cortisone 200 mg. daily and ACTH 150 mg. daily. I shall describe briefly our findings with lesions evoked by (1) tuberculin (P.P.D.), (2) manganese butyrate, which when injected intradermally, causes lesions with the same gross appearance as does tuberculin, but whose causal mechanism does not involve hypersensitivity, (3) atropine in sensitive subjects, (4) histamine, morphine and, in sensitive subjects, grass pollen and cat scurf.

(1) *Tuberculin.*—Using repeated tests with single dilutions of P.P.D. and variable doses of cortisone and ACTH, we were unable to satisfy ourselves that there was any consistent change attributable to treatment; the lesion sizes varied greatly even in control periods. This seems to have been the experience of others using similar methods. Experiments then showed that in man—as Wadley (1949) and Long and Miles (1950) have shown in animals—there is an approximately linear relationship between the lesion diameter and the logarithm of the dose of P.P.D. injected. Our method consisted in making

3-4 series of injections of several dilutions of P.P.D. in each patient in fortnightly periods before, during and after treatment. The mean regression lines were calculated from this data for each period and their positions were compared. The details of this method are described elsewhere (Lovell *et al.*, 1953).

Using this serial dilution method of testing and the relatively large doses of cortisone and ACTH, we found the reaction to P.P.D. was diminished in the 8 patients tested; the diminution was statistically highly significant in every case but one. The reactions sometimes remained diminished until a month after stopping treatment. As Long and Miles (1950) indicated in their guinea-pig studies, with data of this sort it is possible to express numerically the factor by which reactivity to P.P.D. is altered during treatment. In our cases, the factor by which reactivity was reduced was very variable, ranging from 15 to 170.

(2) *Manganese butyrate*.—As with P.P.D., we found that the diameter of the lesions bore an approximately linear relationship to the logarithm of the dose injected, and the reactions were studied by the same method I have described for P.P.D. The reactions were reduced by cortisone or ACTH in all the 9 patients tested. The changes were smaller than those with P.P.D. responses and did not attain statistical significance in 4 cases. The factors by which reactivity was reduced were remarkably consistent, being about two.

(3) *Atropine*.—In 2 sensitive subjects, repeated patch tests and instillation of eye-drops during cortisone treatment caused no inflammatory reactions, though these measures evoked reactions before and after treatment.

(4) *Histamine, morphine, pollen and cat scurf*.—In studying the triple responses evoked by these substances, we made use of the approximately linear relationship between wheal diameter and the logarithm of the concentration which Squire (1950) showed to exist, when pricks were made through histamine and horse dandruff solutions placed on the skin. We found no effect on these lesions with cortisone or ACTH.

The effects of an antihistamine substance provide a contrast with those of cortisone. We found that while promethazine reduces the size of histamine wheals, it does not influence the size of P.P.D. or manganese butyrate responses. From these studies we conclude:

(a) That the mechanisms involved in the development of the triple response, which include the release and effects of histamine, are refractory to the action of cortisone and ACTH; this is true whether or not a hypersensitivity reaction initiates the triple response.

(b) Cortisone and ACTH diminish reactivity to a direct irritant, manganese butyrate, only slightly. The approximately twofold reduction in reactivity is of an order comparable to that described by Järvinen (1951) for the reduced reactivity to ultraviolet light which is caused by cortisone.

(c) In sensitive subjects, reactivity to injected P.P.D. and to atropine ointment and eye-drops is diminished conspicuously.

It seems therefore that, in man, the chain of events comprising delayed inflammations—the sort evoked by manganese butyrate and P.P.D. as opposed to the triple responses—contains a link which is vulnerable to the effects of cortisone and ACTH. We do not know what this vulnerable link is.

One concept of this delayed sort of inflammation may be stated simply, and perhaps wrongly, thus: tissues are injured directly in the case of manganese butyrate and ultraviolet light, and as the result of a hypersensitivity mechanism in the case of tuberculin and atropine. As a result of this injury, diffusible chemical substances are liberated which evoke the tissue changes we recognize as inflammation, namely dilatation and increased permeability of blood vessels and cellular aggregations. Cortisone might interrupt this process at any point. The fact that delayed inflammations due to direct damaging agents and to hypersensitivity mechanisms are both diminished might be held to favour the suggestion that cortisone acts at some stage beyond the causal process itself; for instance it might modify either the release of leucotoxin-like substances, or the responses to such substances. Our attempts to measure the release of such substances have, so far, failed. On the other hand, the hormone effect in man seems to be most conspicuous when the cause of the experimental inflammation involves a bacterial or contact type of hypersensitivity mechanism. This might be held to suggest an effect of cortisone on an immunological mechanism concerned in initiating the delayed sort of hypersensitivity response. At present, however, we feel that in man there are insufficient grounds for attributing reduced tuberculin reactivity to such an "anti-allergic" effect of cortisone, though the possibility of such an effect certainly exists. The elucidation of these problems will require studies with less complex processes than inflammation, and will demand a more detailed knowledge of the mechanisms involved in the bacterial type of allergy.

The experiments mentioned were made with Drs. H. C. Goodman, B. Hudson, P. Armitage and Professor G. W. Pickering.

REFERENCES

- JÄRVINEN, K. A. J. (1951) *Brit. med. J.*, ii, 1377.
 LONG, D. A., and MILES, A. A. (1950) *Lancet*, i, 492.
 LOVELL, R. R. H., GOODMAN, H. C., HUDSON, B., ARMITAGE, P., and PICKERING, G. W. (1953) *Clin. Sci.*, 12, 41.
 SQUIRE, J. R. (1950) *Clin. Sci.*, 9, 127.
 WADLEY, F. M. (1949) *Amer. Rev. Tuberc.*, 60, 131.

Dr. A. J. Järvinen
 Dermatologist
 cases due to the
 the cells
 Dr. H. V. M.
 to treat.
 As usual
 will indi
 left wrist
 from cos
 of cream
 sleep wit
 insectic
 tough so
 But I mu
 Hurst ca
 for most
 up and a
 to use co
 the trou
 applicat
 penicillin
 and the
 had been
 to be ca
 For so



Fig.

Section of Ophthalmology

President—Professor W. J. B. RIDDELL, M.D., F.R.F.P.S., F.R.S.Ed.

[December 11, 1952]

DISCUSSION ON THE ASSOCIATION OF EYE AND SKIN DISEASES

Dr. Alice Carleton, Department of Dermatology, The Radcliffe Infirmary, Oxford: *Contact Dermatitis of the Lids.*—When dermatitis affects the lids only or chiefly, it is in the great majority of cases due to a contact irritant. Of course, a blood-borne toxin or drug or irritant may limit its effects to the lids, because the skin here is sensitive, or, in some cases, because a previous irritation has left the cells with diminished resistance. There is also that curious redness and oedema of the lids which Dr. H. W. Barber has described, which makes its appearance about the menopause and is so difficult to treat. None the less, in the majority of cases we are dealing with a reaction to an irritant contact. As usual with this condition in whatever part of the body it is seen, common sense and imagination will indicate the most likely source of trouble. Just as a dermatitis of the ear lobes, centre thighs and left wrist is most often due to nickel, so a dermatitis of the lids is likely to derive in the first place from cosmetics, not only eye shadow applied to the lids or mascara to the lashes, but the whole range of creams, powders and lotions used on the face, and also nail varnish, specially in those women who sleep with a hand tucked under the face. Next come dusts and volatile fluids used for cleaning, or as insecticides or as a perfume spray or maybe a nasal spray. Dyes applied to the hair often leave the tough scalp uninjured but flare up the surrounding skin, or the dye may come from gloves or furs. But I must confess that the cases most commonly referred to a skin clinic are what the late Sir Arthur Hurst called iatrogenic, that is due to the physician (Fig. 1). I do not mean that doctors are responsible for most cases of facial dermatitis, but that in the nature of the case, these are the ones that do not clear up and are said "not to respond to treatment". If a woman gets a rash on her face, she generally ceases to use cosmetics. Dyeing one's hair, or using insecticide sprays are not things we do daily. But when the trouble is due to eye drops or lid creams, the patient redoubles his or her zeal and puts on the application with greater frequency and increasing damage. The four chief criminals are creams of penicillin, or the sulphonamides, anaesthetic or analgesic creams, especially benzocaine or procaine, and the antihistaminics. Anthisan cream is immensely popular now. I saw a case recently where it had been advised for pruritus vulvæ and where the resultant oedema was so severe that the woman had to be catheterized for three days (Fig. 2).

For some years now, I have been campaigning among the practitioners in my region against the



FIG. 1.—Granuloma due to cough mixture containing potassium iodide.



FIG. 2.—Dermatitis due to Anthisan cream.

Correction.—*Proceedings*, Vol. 46, p. 265, April 1953:

The picture labelled Fig. 2 should be Fig. 1.—"Granuloma due to cough mixture containing potassium iodide."

The picture labelled Fig. 1 should be Fig. 2.—"Dermatitis due to Anthisan cream."

local application of the sulphonamides and penicillin, on the ground that both are potent sensitizers, and that once this has happened, the individual may be precluded from using the drug when it might be urgently needed for a general condition. But evidence is now accumulating that the drawbacks are still more serious. Once a cell has become sensitized to a particular antigen, it tends to make a similar response to other members of the same chemical family. Take for instance the para-group, whose members have an amino group in the para-position. This is a big family and includes the sulphonamides, local anaesthetics of the benzocaine or procaine type, paraphenylenediamine, which is used for dyeing hair and furs, para-aminobenzoic acid and para-aminosalicylic acid, used in conjunction with streptomycin in the treatment of tubercle, and the azo-dyes employed in colouring food stuffs, materials, and nylon stockings. Cases have now been reported of women who have reacted to sulphonamide creams, and who later developed a dermatitis of the legs from the azo-dye in their nylons, or who got a rash on the face and neck from the paraphenylenediamine in their furs.

This whole field is now beginning to be explored, and it is one of great potential interest to us as doctors. A firm might deny liability for an occupational dermatitis on the ground that the original sensitization was induced by medical treatment. Or a furrier might take an action for damages because, following the use of benzocaine or sulphonamide cream, he had been forced to abandon his skilled occupation. There is a whole range of disturbing possibilities.

Let us now imagine ourselves faced with a dermatitis of the lids which we think is probably caused by a contact. The first step is a meticulous case history, and, ideally, a visit to the home of the patient. Usually the next step is to do a patch test, and I feel, perhaps wrongly, that it is a step adopted with more enthusiasm by ophthalmologists than dermatologists. Every dermatologist knows from sad experience that, given a case which subsequently turns out to be due to X, patch tests may be positive to A or B or C, though A, B and C, like the flowers in spring, "have nothing to do with the case". Even more confusing, X, the real criminal, may give a negative response. If then a positive result has no significance, and a negative result does not exclude the substance in question, and this happens not once but often, no wonder the harassed dermatologist gets disillusioned. Skin tests, like many other tests, are useless or even misleading unless one fully understands the kind of information they can give, and the fallacies implicit in them. An excellent account of this was given at the Allergy Section of the American Medical Association by the President, Dr. Feinberg. He pointed out that the treatment of allergy is liable to get into disrepute if absurd or excessive claims are made for it. Many doctors believe that a positive skin test implies a specific immunological reaction to a substance, and that this substance is the cause of the disease. In Dr. Feinberg's words "*Adherence to this belief has resulted in more mismanagement of allergy and greater discredit to the field than any other misconceived notion*". To start with, a positive patch or scratch test may not depend on an antigen-antibody reaction at all. Certain substances, like histamine and codeine, are notoriously urticariogenic. Testing extracts, especially of foods, may be chemically irritating. Or the patient may be one of the 5% who react to mechanical stress by whealing, or dermatographism. Such people will give an apparently positive response to nearly everything. Even if the reaction is immunological, it may not be significant, and this is especially true of food stuffs. The digestive juices destroy so much of the potential antigen that a very large amount has to be eaten in order to reach an operative level. In short, the patient has a slight sensitization, but never gets enough into the blood stream for any abnormal effect. Furthermore, the skin may continue to give a positive response to foods which have long since become innocuous. Babies in their first year are often sensitive to foods, whereas in their second year they more often react to inhalants. But on the ground of positive tests for milk, eggs or wheat, they are sometimes condemned to a diet so restricted as to be inadequate for growth. Again, a positive patch test may be due to cross sensitization. If a patient reacts to wolf hair, we do not need to scan the country anxiously for wolf packs, it only means that the individual is sensitive to dog hair, which is closely allied to the hair of the wolf.

To sum up: a positive patch or scratch test *alone* is of very little value, but if it fits in with the history, we have a valuable pointer. We can clinch the matter by eliminating the supposed antigen, noting the result, and if the dermatitis clears up, submitting the individual to a fresh exposure and again noting the response. What we must NOT do is to tell the patient on the ground of a positive response, *without* an elimination test, that he is never again to eat eggs or drink milk, or the like.

Supposing now that we have an unequivocal case of contact dermatitis, should one now proceed (as we are often asked to do) to hypodermic desensitization? Dr. Feinberg's answer is "NO", if there is any other method available. If simple avoidance is possible, then choose that. With foods, oral desensitization by the ingestion of minute quantities is far preferable. There are some substances which it is impossible to avoid, such as dust or pollen. Here we have no satisfactory option. But the patient should be warned that the treatment is very slow, may not be completely successful and even if it is, cannot give more than temporary results. Nor is desensitization without danger. In a case of a woman who had psoriasis involving the skin near the eyes the skin was tested and found to be sensitive to fish. Without further ado, hypodermic desensitization was begun. The result was a severe, almost necrotic, erythema multiforme, which necessitated hospitalization for six weeks (Fig. 3). The woman who had hitherto eaten fish with impunity, could not now absorb more than a mouthful without a sharp reaction.

Monsi
in the m
shoals.

BARBER

Mr. J
ocular le
latter rel
from der
was to b
Peter Bo

Having
systemic
other dis
tioned w
neuroder
blepharit

Rosace
diagnosis
however,
while to
attack th
shaped o

Many
changes a
the attitu
from rosa
of work d
of that s

of success
the point
found to
new form
success w
nowadays
migrainou
of sterile
examinati

Blephar
then clear
Among c
conjunctiv
in consequ
on plying
several tir
lotion, th

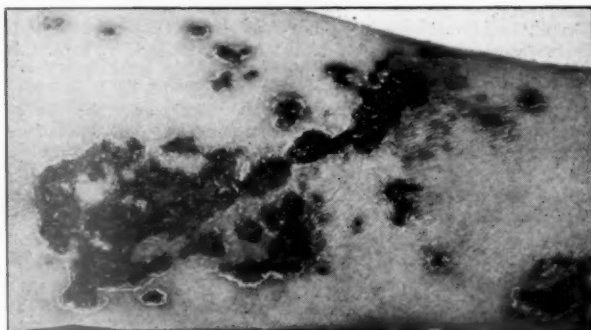


FIG. 3.—Toxic eruption following effort at desensitization to fish.

Monsignor Ronald Knox once said of theological dogmas that they have little interest for the boat in the middle of the stream, they are only there to warn the incautious navigator off theological shoals. What I am trying to do is to plant a few red flags on dermatologic and allergic sandbanks.

REFERENCE

BARBER, H. W. (1946) *Practitioner*, 156, 333.

Mr. J. H. Daggart pointed out that examination of a patient's skin often supplied the clue to an ocular lesion. Admittedly an eye condition sometimes accounted for abnormality in the skin, but the latter relationship is less frequent. In other words ophthalmologists are less able to teach than to learn from dermatologists, and therefore Mr. Daggart considered that his main function at this meeting was to be a bridge between the opening remarks of Dr. Alice Carleton, and the contribution of Dr. Peter Borrie.

Having drawn attention to the wide variety of physical signs in the eyelids, and their linkage with systemic disorders Mr. Daggart proceeded to show pictures illustrating the complications of skin and other diseases which may become manifest in the eyes and their adnexa. Among the conditions mentioned were palpebral gumma, herpes zoster implicating the eyelids, cataract in association with the neurodermatoses, and fundus lesions characteristic of epiloia. He then went on to consider rosacea and blepharitis.

Rosacea.—Most of the victims of rosacea escape corneal ulceration. If the cornea is attacked, diagnosis will, as a rule, be obvious by reason of the associated facial efflorescence. In some patients, however, severe keratitis may arise in the absence of any conspicuous facial signs; then it is worth while to notice the mode and distribution of the corneal involvement. Rosacea is especially prone to attack the lower half of the cornea, and the resulting vascularized opacities are commonly wedge-shaped or tongue-shaped.

Many years ago Professor R. J. V. Pulvertaft remarked that fashion in medical treatment is liable to changes as revolutionary as those which adorn the history of fashion in women's clothes. Certainly the attitude of our profession towards rosacea supports that generalization. Thirty years ago sufferers from rosacea were being treated on an increasing scale with dilute hydrochloric acid on the strength of work done by Ryle and Barber, who had shown that the typical victim secreted inadequate quantities of that substance in the gastric juice. Good results were claimed for this therapy, but that measure of success can now be more rationally explained. The average sufferer from rosacea is meticulous to the point of obsessionism, and intensely susceptible to suggestion. Such a temperament is commonly found to be linked with hypochlorhydria, and the possessor is apt to be greatly encouraged by some new form of treatment, especially if it be administered with sympathy. It will be recalled that similar success was claimed a quarter of a century ago for ultraviolet light therapy—a method seldom used nowadays for ocular rosacea. The same considerations apply to headache. Alleged sufferers from migrainous, post-traumatic and many other forms of headache often respond favourably to injections of sterile water, provided that this placebo therapy is fortified by careful history-taking and by examinations repeated at short intervals.

Blepharitis.—If blepharitis is found associated with a scurfy scalp and widespread facial seborrhœa, then cleansing of the eyelids should be accompanied by appropriate treatment to the face and scalp. Among children, however, it will be found that most attacks of blepharitis arise from neglected conjunctivitis. Crusts of dried secretion become entangled with the lashes and clog the lid margins in consequence of failure to remove discharge from the inflamed conjunctiva. It is useless to keep on plying such eyelids with lotion and ointment without removing the crusts. Crusts should be removed several times a day if necessary. When such material is too adherent to permit flushing away with lotion, the crusts should be dissolved by means of hydrogen peroxide (10 vol. strength). Then the

external surface of affected eyelids should be painted on each occasion with Tinctorium. This treatment, which was successfully applied to hundreds of children at Swanley in the 1930s, is far more efficacious than penicillin. It is disappointing to find that many practitioners and ophthalmologists still use that irritating remedy, yellow oxide of mercury ointment, for blepharitis.

Dr. Peter Borrie: A diagnostic analysis of some of the cases I have seen at Moorfields Hospital, during the past two years, is shown in Table I. Two points need emphasizing. Firstly, only those cases are included in which, either there was a direct aetiological association between the ocular and cutaneous conditions, or the disease from which they were suffering was entirely cutaneous. Secondly, they were all referred, in the first place, by their general practitioners, to an ophthalmic outpatient clinic, and from there they were sent to me. Thus each patient represents a problem met with in routine ophthalmology.

TABLE I

Disease	No. of cases	Per cent	Disease	No. of cases	Per cent
Rosacea	114	33.0	Contact dermatitis ..	17	4.9
Seborrhœa	98	28.4	Pityriasis capitis ..	7	2.0
Periorbital dermatitis:			Lupus erythematosus ..	6	1.8
Medicamentosa ..	16		Ocular pemphigus ..	3	0.9
Allergic	29		Tuberculosis	2	0.6
Infective	27		Behçet's disease ..	1	0.3
	72	20.9	Miscellaneous	7	2.0
Blepharitis	18	5.2			
			Total	345	100.0

Rosacea.—In this group, all of whom had ocular signs, 58% were women, whereas in the skin department of a general hospital 75% of rosaceous patients are women. The cutaneous manifestations began first in 75% of cases. The only correlation found between the skin and eye signs was that only in the women was severe cutaneous involvement likely to be accompanied by severe ocular rosacea. Treatment of the skin caused approximately a 75% improvement in 75% of the patients, but this did not appear to have much effect on the ocular condition.

Seborrhœa.—I have used "seborrhœa" as a generic term to cover all the cutaneous manifestations found in this metabolic abnormality. It is inaccurate, as the basic change is probably in the quality, rather than the quantity, of the sebum. However, it is preferable to seborrhœic dermatitis, since this is only one of the resulting skin changes and, further, the severest and least common.

There is reason to suppose that the majority of the cutaneous manifestations of seborrhœa are essentially infective. Further, these patients are prone to superadded infections, such as styes and boils. Recent work in America (Rebell and Pillsbury, 1950) and this country (Ricketts, Squire and Topley, 1951) suggests that the usual rapid and efficient autodisinfection of pathogenic cocci by the skin takes place only in the presence of normal sebum. Ricketts *et al.* (1951) went further and showed that the operative factor is the presence of unsaturated long-chain fatty acids in the sebum. It appears that this chemical factor is capable, by itself, of disinfecting the skin of pathogenic staphylococci; that, given an element of desiccation, it will also deal with streptococci; but that is has no effect on *Pseudomonas pyocyanea*.

A rather more direct approach to the problem is being made at St. Bartholomew's Hospital, where direct analysis of sebum from normal and seborrhœic subjects shows that a qualitative difference between the two does exist and preliminary results suggest that this difference may concern the long-chain fatty acids.

A further factor necessary for the normal autodisinfection of the skin is an acid medium and Anderson (1951) has shown that the pH of seborrhœic children is abnormally high.

Periorbital dermatitis.—By periorbital dermatitis, I mean an eczematoid reaction, limited to, or primarily affecting, the eyelids and adjacent skin. I have divided my cases into those due to medicaments, applied directly to the affected tissues; those of an allergic origin, in which the causative factor may have reached the skin in ways other than direct application; and those of an infective nature.

Of the medicamentosa group, half were caused by penicillin applied either as an ointment or as eyedrops.

I have had 3 unusual cases in the allergic group. They were all women, who presented with swollen eyelids and denied that they had ever had any other skin affection. However, on direct questioning, they admitted getting a rash under the metal part of their suspenders. In all three, patch tests were strongly positive and they have remained completely well since avoiding contact with all white metal.

The pathogenesis of allergic periorbital reactions is now beginning to be understood. (Edema of this region does not follow intravenous injections of histamine in animals. If, however, a histamine-liberator is injected (Feldberg, 1953), one of the areas to show the greatest swelling is the periorbital. Similarly, if a dye is injected into the bloodstream before the histamine liberator, the periorbital region will be among the most deeply stained areas subsequently. And, finally, quantitative analysis of the histamine content of varying areas of skin shows that the periorbital region contains a disproportionate amount.

Infect
appears
conditi
from ov
age of

Blep
Conda
ophthal
and half

Pityri
might be
the most
called P
reported
have gro
or sebor
than fro
evidence

It may
also bee
exfoliat

Lupus
which af
These ca
distingui
crusting;
slight, ir

Ocular
dermatiti

Tuberc
to the tu
lesions o
phlycten
in skin d
Behçet'
needle, it
case, may

This an
problems
dermatiti
of the che
providing
from diss

ANDER
FELDBER
MARTIN
REBELL
RICKETT
ROCHA,

Mr. G. T.

Miss B.
Referen
diagnos
History
by a donk
she notice
General
On exam
the limit
the skin an

Infective periorbital dermatitis has been called, in America, infectious eczematoid dermatitis. It appears to be an eczematous reaction to the local presence of bacteria, usually staphylococci. The condition may follow irritation of a purulent infection and I have seen a number of cases resulting from over-enthusiastic hot bathing of styes. One-third of these cases occurred in children under the age of 10.

Blepharitis.—These were cases in which I could find no other cutaneous abnormality.

Contact dermatitis.—The periorbital involvement for which these cases were referred to the ophthalmologist was part of a widespread contact dermatitis, half the cases being due to medicaments and half to industrial hazards.

Pityriasis capitis.—These cases were referred to me because it was considered that the dandruff might be aggravating the ocular condition. Pityriasis capitis consists of the continual exfoliation of the most superficial layer of the epidermis of the scalp, in the scales of which can be found a fungus, called *Pityrosporum ovale*. Recently, a number of investigators, both here and in America, have reported finding this organism in between 69% and 100% of normal scalps. Rocha *et al.* (1952) have grown the fungus successfully, but have been unable to produce any lesions with it in normal or seborrhoeic individuals. Martin-Scott (1952), who obtained more positive cultures from normal than from dandruff scalps, was also unable to demonstrate any pathogenicity of the organism. The evidence suggests, therefore, that *P. ovale* is a harmless saprophyte.

It may be of interest in passing, especially to those engaged on research, to note that *P. ovale* has also been cultured from a golden spaniel, a 14-year-old male llama and a rhinoceros suffering from exfoliative dermatitis.

Lupus erythematosus.—There is a distinct clinical variety of chronic cutaneous lupus erythematosus which affects, in a linear fashion, the margin of the lower eyelid, while sparing all the rest of the skin. These cases are usually referred to the ophthalmologist with a diagnosis of blepharitis. Helpful distinguishing factors are the lack of variability over months or years: the absence of oozing and crusting; the loss of the cilia, despite the absence of any folliculitis; and atrophy, evidenced by a slight, irregular, moth-eaten appearance of the lid margin.

Ocular pemphigus.—1 of these 3 cases was the result of erythema multiforme and the other 2 of dermatitis herpetiformis.

Tuberculosis.—Both these cases fall under the heading of tuberculide, a hypersensitive skin reaction to the tubercle bacillus. One was entirely cutaneous; he came to an eye hospital because of a few lesions of the condition on the eyelids. The other was a case of Bazin's disease associated with phlyctenular conjunctivitis. Thus, this much-invoked aetiological factor appears to play little part in skin disease seen in eye hospitals.

Behcet's disease.—When the skin of a patient suffering from this condition is pricked with a sterile needle, it reacts in about thirty-six hours with a pustule. This test, which was positive in the present case, may be of diagnostic help.

SUMMARY

This analysis of the meeting ground of Ophthalmology and Dermatology does show that our common problems are indeed common. Over 80% of my cases suffered from rosacea, seborrhoea or periorbital dermatitis. As clinicians, our job is not so much to solve the problem as to define it for the consideration of the chemists, biochemists, pathologists and pharmacologists. In this way real progress can be made, providing always that we can keep our learned brethren to the point at issue and prevent them from dissipating their energies on exfoliating rhinoceri.

REFERENCES

- ANDERSON, D. S. (1951) *Brit. J. Derm.*, **63**, 283.
 FELDBERG, W. (1953) *Proc. R. Soc. Med.*, **46**, 256.
 MARTIN-SCOTT, I. (1952) *Brit. J. Derm.*, **64**, 257.
 REBELL, G. L., and PILLSBURY, D. M. (1950) *J. invest. Derm.*, **14**, 247.
 RICKETTS, C. R., SQUIRE, J. R., and TOPLEY, E. (1951) *Clin. Sci.*, **10**, 90.
 ROCHA, G. L., SILVA, C., LIMA, A. O., and GOTO, M. (1952) *J. invest. Derm.*, **19**, 289.

Mr. G. T. Willoughby Cashell: *Pseudo Tuberculoma Silicoticum* (case report).—

Miss B. H., aged 42.

Referred from the Dermatological Department by Dr. H. T. Calvert on October 28, 1952, with a diagnosis of pseudotuberculoma silicoticum.

History.—A lump appeared recently in the upper and lower eyelid in the site of a scar from a kick by a donkey at the age of 5. The scars started to irritate about a month prior to examination and then she noticed the swelling in each eyelid.

General health.—Good up to a year ago when she felt a little off colour.

On examination.—There was a slightly raised reddish tumour in the middle of each lid just outside the limit of the tarsal plates. Under the swelling in the upper lid was an extensive tumour attached to the skin and to deep structures. Similarly there was a small tumour under the skin of the lower lid.

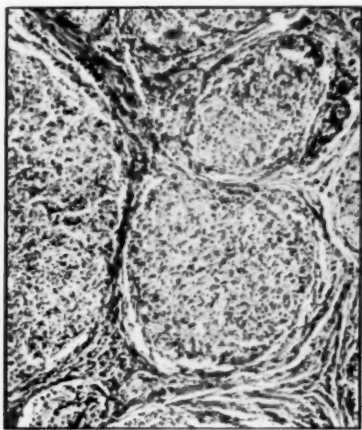


FIG. 1.—Follicular arrangements of epithelioid cells and fibrous trabeculae surrounding the follicles. $\times 68$.

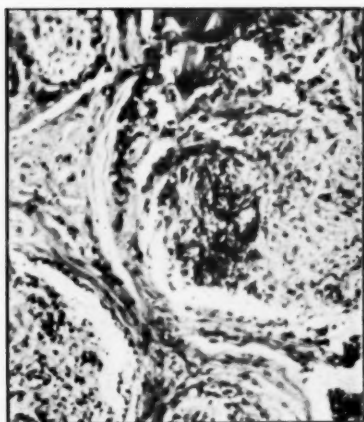


FIG. 2.

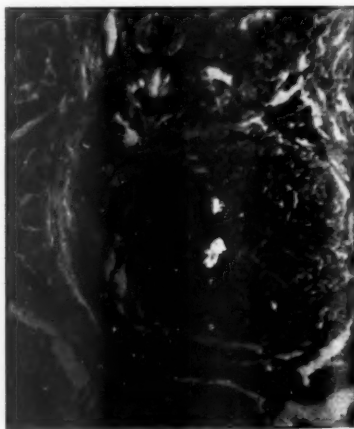


FIG. 3.

FIGS. 2 and 3. A giant cell.—3 shows the same field as 2. Photographed through polaroid. The granules in the centre of the giant cells are doubly refractile. $\times 80$.

the tumours, and to Dr. B. A. Bembridge for reporting on the sections and producing the photographs.

General Discussion.

In reply to Dr. E. S. Perkins, who asked what percentage of patients reacted to penicillin drops, Dr. A. Carleton said that patients were much more liable to be sensitized by creams than by drops. In perhaps 20% or less of the cases the penicillin had been used as drops. When tests were made there had been very confusing results. For example, in certain cases penicillin and the cream base had each given a negative result when applied separately, but the two together a positive result.

Dr. R. W. Stephenson (Cheltenham) said that in the days when penicillin first came into general use, perhaps some of them were over-enthusiastic in their resort to it and consequently the results, apparently, varied from place to place. Thus, whereas in Oxford the surgeons said that they generally found penicillin sensitivity, in Cheltenham penicillin sensitivity was very rarely found.

The President said that the variations might be due to the small numbers involved.

Mr. F. A. Williamson-Noble said that blepharitis seemed to be much more common among blind people. Was it possible that in these cases an unusual amount of ultraviolet light got through the skin, and affected Warburg's yellow enzyme? In certain cases vitamin B had been given and the results were fairly satisfactory.

November 7, 1952 (Mr. St. Clair Roberts): The skin swellings and the deeper tumours were excised. The tumours were lobulated, attached to the surrounding structures and also to the periosteum of the orbital margin above (Figs. 1, 2, 3).

Tests.—Mantoux: 1 : 10,000, 1 : 100,000 negative.

X-ray: Chest and hands negative to sarcoid.

Plasmas: Protein 5.9, albumin 2.3, globulin 3.6%. A/G. ratio 0.6 : 1.

This appears to be a case of pseudotuberculosis silicoticum originally described by Shattock in 1917.

Other descriptions of similar cases produced by talc powder in abdominal wounds have also been reported from time to time.

The characteristics of this particular type of lesion are: (1) The long latent period from the time of the injury to the appearance of the cutaneous changes. (2) The sarcoid-like lesions involving the skin and subcutaneous tissue. (3) The presence of doubly refractile granules in the giant cells. (4) The absence of any other signs of sarcoidosis or tuberculosis.

Thanks are due to Dr. H. T. Calvert for referring the case, to Mr. St. Clair Roberts, my Registrar, for excising

Endocar

The cl
to be re
wider co
some of
was atta
made in

Case r
and deliv
twins we
a larger a
normal,
pattern.

June v
broncho

On ad
audible a
her cond
was found
to be a s

She be
She wa
of pneum

On ad

There wa
edge was
in the lun
gradually
this time
overlook
showed a

During
2 years,
twenty-f

On ad
and sligh

The liver
X-ray sho
a sinus ta
and she v

On this si
70-80, an
a few mo
readm (te

most strik
days but
irritable a
of orthop
same tim
tachycard
previous

Octob
Dr. R. E.
it was th

APRIL

Section of Pædiatrics

President—D. W. WINNICOTT, M.A., F.R.C.P., M.R.C.S.

[October 24, 1952]

Endocardial Fibro-elastosis in One of 3-year-old Twins.—J. J. KEMPTON, M.D., M.R.C.P.

The clinical picture produced by this disease in cases which survive early infancy is only now beginning to be recognized, and with this recognition and more detailed anatomical and pathological studies, a wider concept of the disease process is being developed to include that of fetal endocarditis and also some of the cases to which, previously, the unsatisfactory label of idiopathic cardiac hypertrophy was attached. It is suggested that a clinical diagnosis of endocardial fibro-elastosis may justifiably be made in the following case.

Case report.—June M., aged 3 years 2 months, was a premature twin. Birth-weight was 4 lb. 12 oz., and delivery and the neo-natal period were normal. Details of placenta are not available, but the twins were thought to be identical, and had the same birth-weight. The other twin, Irene, has become a larger and more sturdy child and has had no serious illnesses; her heart is clinically and radiologically normal, as is her electrocardiogram. Thumb prints of the twins show a considerable similarity of pattern. Four elder children and the parents are healthy.

June was first admitted to the Battle Hospital, Reading, at the age of 3 months with a diagnosis of bronchopneumonia after two or three days' pyrexia, cough and increasing respiratory distress.

On admission she was febrile and very slightly cyanosed with a rapid respiratory rate. Râles were audible all over the lung fields. Her liver was enlarged. Penicillin and oxygen were administered and her condition improved slowly. Three days after admission her liver was no longer palpable. She was found to be anæmic with Hb of 50% and was put on iron. This illness was, at the time, considered to be a simple respiratory infection.

She began to walk at 1 year.

She was sent into the Royal Berkshire Hospital at the age of 15 months, again with the diagnosis of pneumonia.

On admission she was febrile and in fairly severe respiratory distress with a respiratory rate of 70–80. There was a mucopurulent nasal discharge, and râles were audible all over the lung fields. Her liver edge was felt about three fingers below the costal margin. X-ray showed extensive mottled opacities in the lung fields, and an enlarged heart shadow. Her heart-rate on admission was 170–180, and this gradually subsided to a normal rate. The possibility of paroxysmal tachycardia was considered at this time; it was thought that a period of more rapid rate might have preceded admission or been overlooked. Re-X-ray a month after admission, when there were no abnormal physical signs, still showed an apparently enlarged heart shadow. Pancreatic tryptic activity was found to be normal.

During the next three months the mother noticed occasional slight breathlessness. At the age of 2 years, she was again sent into hospital with a history of six days' increasing breathlessness and twenty-four hours' persistent vomiting.

On admission.—Definite picture of cardiac failure with marked respiratory distress, orthopnoea and slight cyanosis, and a respiratory rate of 70 to 85. She was afebrile. Her heart-rate was 170–190. The liver was enlarged and there was some jugular venous engorgement and slight peripheral oedema. X-ray showed more obvious cardiac enlargement with extremely congested lung fields. ECG showed a sinus tachycardia with perhaps some evidence of left ventricular preponderance. Oxygen was given and she was put on digoxin 0.25 mg. eight-hourly for three doses, and then 0.125 mg. eight-hourly. On this signs of cardiac failure rapidly disappeared. Within three days her heart-rate had dropped to 70–80, and chest signs and liver enlargement were no longer apparent. Digoxin was discontinued after a few more days. Persisting cardiac enlargement was now clinically apparent. Four weeks later readmitted to the ward with recurrence of signs of cardiac failure. Response to digoxin was again most striking and the signs disappeared in forty-eight hours. The digitalis was stopped after three days but she was kept in hospital, and ten days later a further attack developed. In this she became irritable and distressed towards the evening, and her respiratory rate rose to 80 with the development of orthopnoea and a cyanotic tinge, while râles appeared over the lung fields. Her heart-rate at the same time rose from 90 to 190–200, and an ECG, taken as the attack was developing, showed a tachycardia with no evidence of abnormal rhythm. Response to digoxin was again rapid as on previous occasions.

October 1951: She was transferred to the Hospital for Sick Children, Great Ormond Street, under Dr. R. E. Bonham Carter. The possibility of a paroxysmal auricular tachycardia was considered, but it was thought that, in addition, there must be some intrinsic cardiac condition to explain the fact of

cardiac enlargement which had been shown to persist in the absence of tachycardia, or of signs of failure. A precordial bulge was apparent at this time, and the apex beat was palpably displaced to the left.

Since discharge she has attended Out-patients in Reading, and has been kept on digoxin 0.125 mg. twice daily. The dose was diminished to 0.125 mg. once daily for a short period in July this year, but she is again, at present, on the full dose.

She has steadily improved. She is perhaps a little breathless on exertion, but she runs about and plays actively. X-ray (Fig. 1) still shows considerable cardiac enlargement, which, on screening, seems to be mainly left-sided. The lung fields are much clearer, though on screening it appears that her vascular markings are a little increased. ECG (Fig. 2) shows some digitalis effect and there is evidence of left ventricular hypertrophy. B.P. is 115/70 and previous figures have been similar. She is tuberculin negative. Apart from her early anaemia the blood picture has been normal, and her urine has shown only a trace of albumin during the episodes of failure. E.S.R. was normal on two occasions of acute illness.

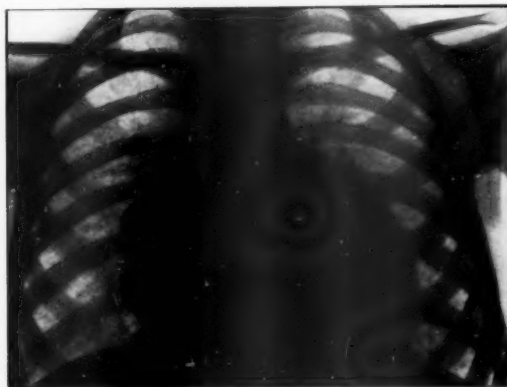


FIG. 1.—Heart shadow showing somewhat globular enlargement, persisting in the absence of tachycardia or signs of failure.

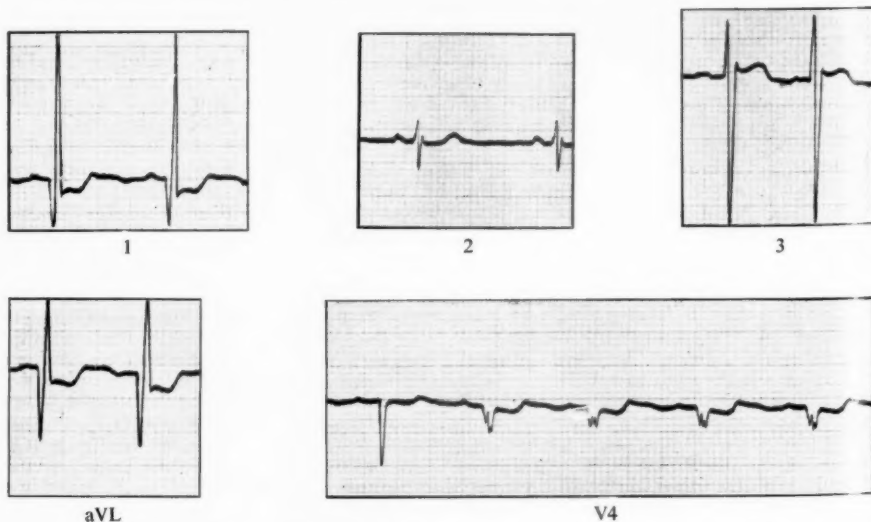


FIG. 2.—ECG of June M. High R and deep Q waves are seen in Lead I and aVL. Digitalis effect is present. Paroxysmal conduction disturbance appears in V4.

The ch
be precip
were ass
persisted
ing symp
evidence
during th

There
has been
of adren
not been
rare, and
of conge
(1947) to
forms of
sided enl

There
In mos
or after t
recorded
the mura

These
her mark
which m

"Foeta
the resul
might ac
by Farbe
infective
review o
had led
openings
elastic ti
Further
studies o
accepted
producing
infancy,
lead to m

It seem
be respon
vessels, c
discussed
43 cases,
6 of which

On the
in this co
in a review
emphasiz

Such a
hypertens
Lew's
sostrin
found in

This la
dominant
diagnos
that a le
can be o
which m
known

The child has thus had repeated episodes of cardiac failure since early infancy, at first seeming to be precipitated by respiratory infection, and later occurring without preceding infection. These attacks were associated with cardiac enlargement which was at first apparently progressive and which has persisted. The episodes of acute illness, with paroxysmal dyspnoea and tachypnoea as the main presenting symptoms, suggest attacks of predominantly left-sided failure, and there is radiological and ECG evidence of mainly left-sided enlargement. There are no cardiac murmurs. No attacks have occurred during the last year, while she had been taking digoxin.

DIFFERENTIAL DIAGNOSIS

There has been nothing in the history or findings in this case to suggest rheumatic carditis, and there has been no evidence of any abnormality of rhythm. Glucose tolerance tests and study of the effect of adrenaline on fasting blood sugar have not been done, and glycogen-storage cardiomegaly has not been excluded. This and other intrinsic cardiac diseases such as rhabdomyomatosis are exceedingly rare, and likely to be rapidly progressive. There are no physical signs to suggest any recognizable form of congenital heart disease: the rare anomalous origin of the left coronary artery is said by Taussig (1947) to produce characteristic ECG changes. Cardiac catheterization could exclude intracardiac forms of left to right shunt, but if such were present one would expect some signs of relative right-sided enlargement, and it is doubtful if the procedure is justifiable at present.

There are no physical or radiological signs to suggest coarctation or a patent ductus arteriosus.

In most of the recorded cases of fibro-elastosis, death has occurred in early infancy, usually suddenly or after too brief an illness for much clinical observation to be possible. Where symptoms have been recorded they have usually pointed to left ventricular failure, and mainly left-sided involvement of the mural endocardium is the most frequent autopsy finding.

These considerations have led to a tentative diagnosis of fibro-elastosis in this case. If it is correct her marked improvement in the last year may be due to improving collateral coronary circulation which may continue to develop for a time.

COMMENT

"Fœtal endocarditis" was considered by Maude Abbott (1908) to be an inflammatory condition, the result of infection during intra-uterine life. She thought, too, that this process in localized form might account for some of the stenotic forms of congenital heart disease. This view was also held by Farber and Hubbard of Boston, who published a review of 14 illustrative cases in 1933. The infective theory was first disputed by another American pathologist, Gross (1941), who, in a general review of the subject with a case report, suggested that the associated myocardial changes which had led to the concept of an inflammatory process could well be produced by obliteration of the openings of the luminal and thebesian vessels by the dense subendocardial layer of fibrous and elastic tissue, and that this latter might be a developmental anomaly.

Further evidence in favour of this conclusion was produced by the anatomical and pathological studies of Wearn (1941) at the Johns Hopkins Hospital; and it now seems that the view should be accepted that endocardial fibro-elastosis is, in fact, due to some sort of developmental anomaly, producing in its severer form the picture of fœtal endomyocarditis, and stillbirth or death in early infancy, and in its milder forms a condition in which a degree of compensation with hypertrophy may lead to more or less prolonged survival.

It seems, too, that though the process is not an infective one it may, as Maude Abbott thought, be responsible for some of the forms of stenotic valvular disease unassociated with transposition of vessels, or septal defect. This is shown, and the nature of the causative embryological aberration is discussed, in a more recent report from Boston by Craig (1949), who reviews autopsy material from 43 cases, in many of which valvular and sub-valvular involvement could be demonstrated, and in 6 of which the process was limited to valves only.

On the clinical side, the wider concept of this disease receives support from 2 case histories reported in this country, that of Vulliamy in 1947, and that of Glynn and Reinhold in 1950. Adams and Katz in a review of 21 cases, including 4 living, have recently (1952) added details to the clinical picture, emphasizing the importance in diagnosis of attacks of left ventricular failure.

Such attacks, with the picture of paroxysmal cardiac dyspnoea, are easily recognized in the adult hypertensive in whom they are expected, but are unfamiliar in infancy, and so are liable to be missed.

Lewis (1951) and other American authors note the effect of digitalis, and it seems that this may be so striking as to constitute in itself a point in favour of the diagnosis, being in contrast to that commonly found in failure in recognizable congenital heart disease.

This last point emphasizes the importance of early consideration of the diagnosis in case of predominantly left-sided failure of obscure cause in infancy, with cardiac enlargement, in which both diagnosable congenital heart disease, and myocarditis, can reasonably be excluded. It seems possible that a degree of gradual compensation may lead to much longer survival if early episodes of failure can be overcome with the aid of therapy, and this applies specially, of course, to the milder cases which may be recognized with increasing frequency as the clinical picture becomes more widely known.

SUMMARY

A case is described in which the diagnosis of endocardial fibro-elastosis seems justifiable in a twin aged 3. Her sister, probably identical, appears to have a normal heart. The diagnosis is discussed and some of the literature is surveyed demonstrating the gradual development of a much wider concept of this disease to include that of foetal endomyocarditis, and many cases of "Idiopathic hypertrophy" as well as some cases of stenotic congenital heart disease.

ACKNOWLEDGMENT

I wish to record my thanks for much help received in this problem from Dr. R. E. Bonham Carter.

REFERENCES

- ABBOTT, M. E. (1908) Congenital cardiac disease. In Osler, W., and McCrae, T., *A System of Medicine*. London: 4, 323.
- ADAMS, F. H., and KATZ, B. (1952) *J. Pediat.*, **41**, 141.
- CRAIG, J. M. (1949) *Bull. int. Ass. med. Mus.*, **30**, 15.
- FARBER, S., and HUBBARD, J. (1933) *Amer. J. med. Sci.*, **186**, 705.
- GLYNN, L. E., and REINHOLD, J. D. L. (1950) *Arch. Dis. Childh.*, **25**, 170.
- GROSS, P. (1941) *Arch. Path.*, **31**, 163.
- LEWIS, K. C. (1951) *J. Pediat.*, **39**, 698.
- TAUSSIG, H. B. (1947) *Congenital Malformations of the Heart*. New York.
- VULLIAMY, D. J. (1947) *Brit. Heart J.*, **9**, 161.
- WEARN, J. T. (1941) *Bull. Johns Hopk. Hosp.*, **68**, 353.

Periarteritis Nodosa.—S. D. V. WELLER, M.D., M.R.C.P.

C. H., girl, aged 6.

Past history.—No relevant family history. At age 3 admitted to an isolation hospital complaining of pains in the legs thought to be due to poliomyelitis. Discharged after four months with a diagnosis of Still's disease.

Present illness.—February 1952 recurrence of limb pains. March 1952 rash on legs and later on forearms, more conspicuous in cold weather. Referred to hospital in June 1952. Skin condition found to be livedo racemosa with innumerable small nodules throughout the area of the rash. Found to have leucocytosis, E.S.R. of 70 mm. in the first hour (Westergren) and inconstant microscopic hæmaturia. Serum proteins 7.6 grammes%, with reversed A : G ratio, and excessive α_2 and γ globulins.

Progress.—Rash remained constant, nodules disappeared and then recurred. Continual low-grade fever and tendency to weight loss. Biopsy in July not diagnostic. Repeat biopsy when nodules had recurred in August, showed disorder of collagen and areas of inflammation associated with blood vessels (see Fig. 1).

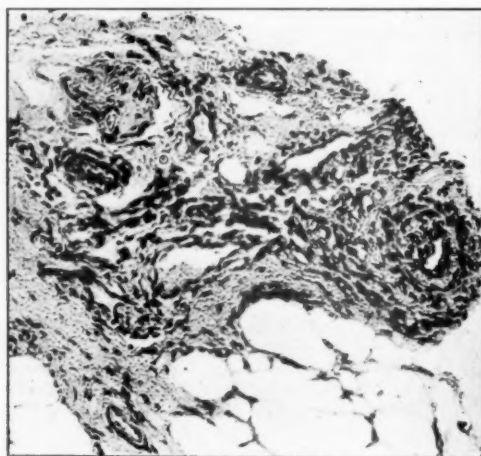


FIG. 1.—Periarteritis nodosa. Skin. $\times 210$.

Purpura and melæna occurred during the period of relapse of the nodules. Moderate anaemia developed. Hypertension and eosinophilia were never recorded.

21.8.52: ACTH started (40 mg. per day) with immediate reduction of fever and general improvement, but with no effect on the rash, which persisted unchanged. E.S.R. fell to normal. (Edema and

moon face rapidly developed, the former being controlled by low salt intake. Serum proteins became normal.

Since treatment, no relapse of nodules. Weight and general good progress have been maintained and the rash is now slowly fading.

The case is almost identical with those reported by Neale, A. V. (1949, *Arch. Dis. Childh.*, **24**, 224).

Peripheral Vascular Disease in a Child.—ROBERT WIGGLESWORTH, M.B., M.R.C.P. (for VICTORIA SMALLPEICE, M.D., F.R.C.P.).

M. S., girl aged 7 years.

Family history.—No similar disease.

History.—March 1952: She developed severe pains in the legs which started in the left calf and a few weeks later also occurred in the right. Swelling of the big toe and transient stiffness of the knee-joint in the right leg soon followed.

1.7.52: Admitted to the Radcliffe Infirmary, Oxford, for investigation. She was pale with a few glands in the neck and axillæ and a lax full doughy abdomen. Spleen was just palpable. Hæmoglobin was 55%, R.B.C. showed considerable anisocytosis and iron deficiency. E.S.R. 22 mm. in first hour (Westergren), and 8 mm. three weeks later. Other investigations were negative. Treatment with Mist. ferri sulph. 3 grains t.d.s. was followed by a reticulocyte response in four days and hæmoglobin rose to 90% two months later. The only complaint was slight aching in the legs after exercise.

9.9.52: A minute area of gangrene appeared on the tip of the right little toe, the size of a pin-head, and the other toes peeled a little. This spread to involve $\frac{1}{4}$ in. of the tip of the toe and she was readmitted to hospital. The only complaints were cramp-like pains on walking and occasional pains in the feet.

On examination.—At room temperature the feet were cold but red in colour. The femoral pulses were palpable as was the left lateral genicular but all other pulses in the lower limbs were absent. In the arms the radial pulses were both absent and other pulses were normal. Blood pressure was 90/50 mm.Hg. Buerger's elevation and lowering test on the right leg produced blanching of the foot in the elevated position in half a minute and cyanotic flushing in the lowered position in the same time.

Investigations.—Urine normal. Hb 81%. W.B.C. 8,700. W.R. and Kahn negative. Blood urea 15 mg.%. X-ray of both legs: no lesion seen. Left femoral angiogram—complete obstruction of the femoral artery. Collateral vessels opened up, especially the lateral genicular artery, but main arteries below the knee not visualized and those seen in lower leg very thin and tenuous (Fig. 1). Tuberculin tests negative. Plasma cholesterol 160 mg.%. Calf muscle biopsy: arterioles normal. Exercise tolerance test: 180 yards walked before onset of pains in both calves which passed off in two to three minutes.



FIG. 1.—Left femoral angiogram showing complete obstruction of the femoral artery above the popliteal fossa. The collateral vessels have opened up, especially the lateral genicular artery, but main arteries below the knee are not visualized and those seen in the lower leg are very tenuous and thin.

Comment.—In this unusual case of peripheral vascular disease in a child there was no evidence of any congenital anomaly. There was no history of physical or chemical trauma, ergot, lead or other poisoning, or of preceding infection. There were no signs of diabetes mellitus or cause of multiple embolism. The absence of hypertension, arterial calcification on X-ray and renal involvement is against the diagnosis of arteriosclerosis. Raynaud's disease usually affects the upper limbs and gives rise to attacks of pallor and cyanosis of the digits on exposure to cold or on excitement. There is no history of such attacks in this child and the arterial abnormality is constantly present. Periarteritis nodosa is an unlikely diagnosis in view of the absence of fever, skin rash, palpable subcutaneous nodules along the blood vessels, absence of renal involvement, leucocytosis and eosinophilia, and lastly absence of peripheral nerve involvement. Pink disease is occasionally associated with gangrene of an extremity and has been described in older children, but there were no signs of this disease in this child. Thrombo-angiitis obliterans remains a possible diagnosis. One case in a child of 2 years in which both legs were involved with gangrene, came to post-mortem and was described by Cahill, J. A., Jr. (1928) *Sth. med. J., Nashville*, 21, 105.

Eosinophilic Granuloma of Skin.—N. R. BUTLER, M.D., M.R.C.P., and M. GARRETT, M.R.C.P. (for BERNARD SCHLESINGER, M.D., F.R.C.P., and P. J. HARE, M.D., M.R.C.P.).

R. M., male, aged 22 months. Developed ulceration of face and scalp on second day of life, spreading to trunk and thighs by 6 weeks of age; successive crops of these ulcers appeared until the age of 14 months. Lesions started as tiny raised transparent papules, then ulcerated within a few hours with formation of scabs which healed spontaneously within two to three weeks. These lesions have now disappeared but since 10 months of age larger persistent areas of ulceration have appeared in the axillae and groins (Fig. 1), together with thickening and abundant granulation tissue around the anal margin. Ulcers are large and indolent with red hypertrophic edges and a base formed of yellow slough, resembling a condyloma. No spontaneous healing, but marked improvement following radiotherapy. (Total dosage 500 r to each lesion spread over two weeks.) There was also a secondary infection of the ulcers with *Staph. aureus*, controlled by oral chloramphenicol. No constitutional reaction, afebrile, and has always gained weight normally. An only child with normal family history. No adenopathy, splenomegaly, anaemia or radiological evidence of bone involvement.

Investigations.—Hb 78%; W.B.C. 9,600 (polys. 65.5%, lymphos. 26.5%, monos. 5.5%, eosinos. 2.5%). E.S.R. 12 mm. in first hour (Wintrobe). Mantoux 1:100 negative. W.R. and Kahn negative. Serum proteins 6.5 grammes% (albumin 4.6 grammes%, globulin 1.9 grammes%, A/G ratio 2.4:1). Serum cholesterol 154 mg.%. Serum cholesterol ester 107 mg.%.

Skin biopsy (aged 20 months) showed an acanthotic epidermis overlying an area of cellular infiltration (Fig. 2) which was free from collagen and elastic tissue, but was pervaded by a meshwork of reticulum fibres (Fig. 3) and surrounded by numerous blood vessels. This pleomorphic infiltrate consisted of large mononuclear cells, giant cells (Fig. 4), lymphocytes, small round cells with deeply eosinophilic cytoplasm and scanty plasma cells. The small round cells when stained with Sudan black were found to contain a lipid which was not neutral fat or cholesterol but gave a PAS-positive reaction suggestive of a phospholipid.

Comment.—The slow and remitting clinical course, biopsy findings and good response to radiotherapy in the present case confirm the diagnosis of eosinophilic granuloma of the skin of which Lever (1949) recognizes three types:

(a) Eosinophilic granuloma of skin associated with typical skeletal involvement, of which four cases have been described, all in infancy or childhood (Curtis and Cawley, 1947; McCreary, 1948; Pinkus *et al.*, 1949; Lever and Leeper, 1950).

(b) Eosinophilic granuloma of skin occurring in adults as solitary plaque-like lesions in the face with no bone involvement.

(c) A heterogeneous group of skin granulomata from various other causes which later may become infiltrated with eosinophils. This group includes pyogenic granulomata, tuberculides, and generalized diseases such as lymphadenoma and periarteritis nodosa.

The appearance, histology, and cause of the skin lesions in the present case closely resemble that of group (a) but there is, as yet, no bone involvement. The basic condition is a lipid histiocytosis, with a similar underlying pathology to eosinophilic granuloma of bone, Letterer-Siwe's disease and Hand-Schüller-Christian disease, the common pathological nature of which was established by Jaffe and Lichtenstein (1944). Various skin lesions are described in this group of diseases, but one form merges frequently into another, as may happen with the other manifestations.

(1) Skin involvements occur in about half the cases of Hand-Schüller-Christian disease, which classically also shows a triad of exophthalmos, granulomatous defects in the skull and diabetes insipidus, with usually a benign course. The skin manifestations may take the form of generalized pigmentation or bronzing, but more often there is xanthoma disseminatum, or lesions characterized by numerous small red papules over trunk and limbs covered by greasy scales or crusts, resembling seborrhoeic dermatitis but sometimes showing a petechial centre.

FIG. 1

FIG. 3

(2) In hood with skin inv ground v and eosin
(3) In consis ponding is by no

CURTIS, JAFFE, H. LEVER, MCCRERY, PINKUS,

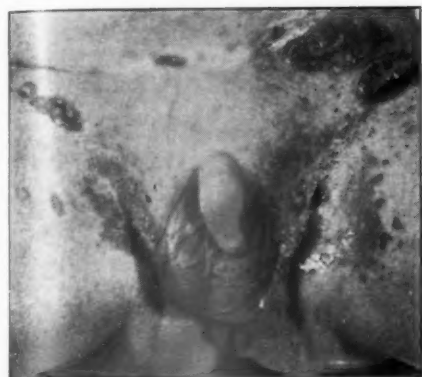


FIG. 1.—Ulcerated areas in groins and anal region.

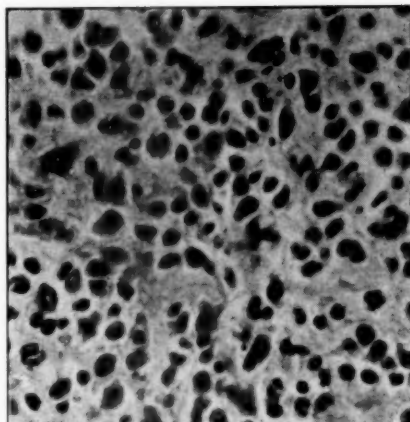


FIG. 2.—Pleomorphic histiocytic cellular infiltrate. \times H.P.

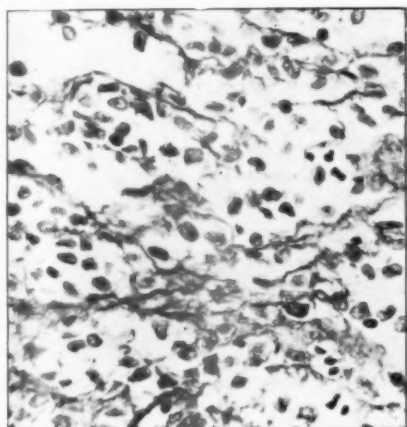


FIG. 3.—Reticulum network enmeshing cellular infiltrate. \times H.P.

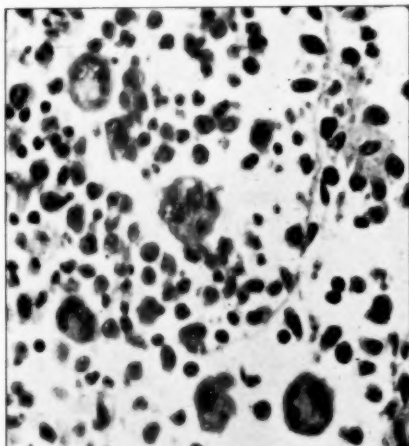


FIG. 4.—Multinucleate giant cells. \times H.P.

(2) In Letterer-Siwe disease, the most severe form of the three, occurring in infancy or early childhood with adenopathy, hepatosplenomegaly, anaemia and bone granulomata, there is nearly always skin involvement. This is usually a generalized haemorrhagic rash with petechiae on a papular background which may later ulcerate. Histologically the skin shows a reticulum containing histiocytes and eosinophils, occurring usually without lipidization as the process is so acute.

(3) In eosinophilic granuloma of bone, skin involvement is rare and in the few reported cases consists of crops of papules which soon become granulomatous plaques and later ulcerate, corresponding closely to those found in the present case, in which the possibility of later bone involvement is by no means ruled out.

REFERENCES

- CURTIS, A. C., and CAWLEY, E. P. (1947) *Arch. Derm. Syph., Chicago*, **55**, 810.
 JAFFE, H. L., and LICHTENSTEIN, L. (1944) *Arch. Path.*, **37**, 99.
 LEVER, W. F. (1949) *Histopathology of the Skin*. Philadelphia and London.
 —, and LEEPER, R. W. (1950) *Arch. Derm. Syph., Chicago*, **62**, 85.
 MCCLEARY, J. H. (1948) *Arch. Derm. Syph., Chicago*, **58**, 372.
 PINKES, H., CAPPS, L. A., CUSTER, S., and EPSTEIN, S. (1949) *Amer. J. Dis. Child.*, **77**, 503.

Letterer-Siwe Disease Controlled by Cortisone.—P. J. N. Cox, B.M., M.R.C.P. (for Professor A. A. MONCRIEFF, C.B.E., M.D.).

I. N., girl, aged 17 months.

First admitted 31.7.51, aged 11 weeks, with history of sudden onset of fever and convulsions on the previous day.

Initial findings.—Temperature 104.8° F., spleen considerably enlarged; no other abnormality; no enlarged lymph nodes. Hb 68%, W.B.C. 14,200, neutros. 56%, lymphos. 44%. Bone-marrow, X-rays of chest and skeleton, Mantoux, W.R., agglutinations against typhoid group and Brucella, blood culture—all negative.

Three days after admission she developed a petechial rash; this became more profuse and after three weeks flat infiltrative papules also appeared. The spleen meanwhile had become enormous. The diagnosis of Letterer-Siwe disease was then proved by skin biopsy and splenic puncture.

Histological report (Dr. Martin Bodian).—*Skin lesion* (Fig. 1): In the upper layers of the dermis there is a circumscribed area of dense infiltration with cells of the reticulo-endothelial series; many of these cells have large pale-staining ovoid or folded nuclei, whilst others have darker staining lobed nuclei like blood monocytes. The cytoplasm of adjacent cells tends to fuse in some areas, thus giving the impression of early syncytium formation. Eosinophils are not present and there is no evidence of necrosis or deposition of lipid. Mitotic figures are common.

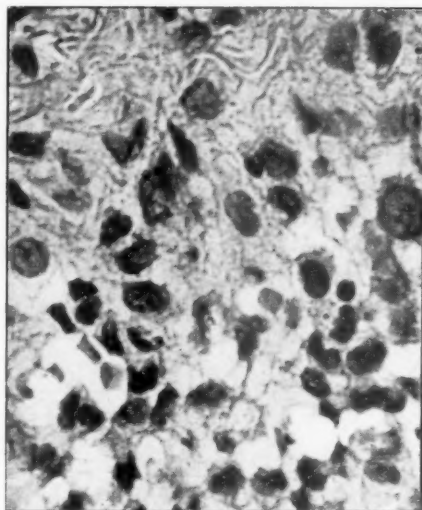


FIG. 1.—Skin lesion,
× 600.

Splenic puncture: Appearances similar to those in the skin biopsy.

Treatment.—A ten-day course of chloramphenicol had already been given before the diagnosis was known; this was accompanied by a fall in temperature, but the spleen continued to increase in size and a few days after treatment was stopped the temperature rose and a fresh crop of spots appeared. Chloramphenicol was given again for five days and streptomycin for six days, without response.

1.9.51: Cortisone 40 mg. per day intramuscularly. Temperature fell within a few days, rash gradually faded and spleen became smaller. Blood transfusion also given as Hb had fallen to 50%, and platelet count to 30,000; atypical mononuclear cells seen in blood films. Dose of cortisone gradually reduced and stopped on 17.12.51. (First course fifteen weeks with one gap of seven days during which chloramphenicol again given owing to gastro-enteritis.)

11.2.52: Readmitted in severe relapse. Febrile; rash as before; spleen larger. Marked cyanosis, believed to be due to pulmonary infiltration. X-ray chest showed faint diffuse mottling of lung fields. E.S.R. 2 mm. in first hr. (Westergren). X-ray skeleton normal.

Cortisone 40 mg. per day intramuscularly started immediately; dose increased to 100 mg. per day on 19.2.52. General condition gradually improved, cyanosis disappeared in two weeks, rash at first became more profuse and then faded; spleen diminished in size but remained palpable.

20.3.52–20.4.52: Gradual reduction of cortisone from 100 mg. per day intramuscularly, to 12.5 mg. per day orally.

20.4.52 to March 1953: Maintenance dose of cortisone 12.5 mg. per day orally continued. Spleen has remained palpable and she has had occasional small crops of typical papular lesions, but general health good and weight gain normal. No anaemia.

Comm
bone are
single pa
in patho
Siwe dis
disease
of prolo
R. P., 19
The ca
and trea
serious
been no
granulom
Treat

Turner's
C. W.
year, su
Famil
epicanth
Early
and feet
Slow
with no
Recent
Difficult
Physic
Pubis to
Dimer

Fi
APRIL

Comment.—Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophil granuloma of bone are conditions with so much in common that they may justifiably be regarded as variants of a single pathological process (Farber, S., 1941, *Amer. J. Path.*, 17, 625). In spite of this common ground in pathology and the not infrequent occurrence of intermediate forms the clinical picture of Letterer-Siwe disease remains relatively clear cut and it is generally agreed that, unlike Hand-Schüller-Christian disease and eosinophil granuloma of bone, the condition is usually rapidly fatal. The only other report of prolonged remission or recovery is that of a case which was treated with streptomycin (Aronson, R. P., 1951, *Lancet*, 1, 889).

The case under discussion has now shown a striking clinical response to cortisone on two occasions, and treatment has continued for periods of three and a half months and thirteen months without serious complication. In spite of the apparent change in the clinical course of the disease there has been no evidence of progression to the formation of lesions resembling the more benign eosinophil granuloma of bone.

Treatment will be continued in the hope that complete spontaneous recovery will eventually occur.

Turner's Syndrome with Coarctation of the Aorta.—D. G. VULLIAMY, M.D., M.R.C.P.

C. W., girl, aged 8 years. She was under the care of Dr. R. C. Mac Keith at Guy's Hospital for one year, suffering from recurrent headache and vomiting, and retardation of growth.

Family history.—Parents normal. Sister, aged 10 years, normal except for presence of wide medial epicanthic folds. Sister, aged 6 years, normal and taller than the patient.

Early history.—Normal pregnancy and birth, weighing 5 lb. 10 oz. Unexplained œdema of hands and feet at birth, persisting in the feet for first three years.

Slow gain in weight (17 lb. at 20 months; 22 lb. at 3 years). Walked and talked at normal age, with normal intellectual development.

Recent history.—Headaches, usually ending in vomiting, at one to three week intervals for one year. Difficulty in sleeping at night for one year.

Physical findings.—Height 45 in. Weight 40 lb. Arm span 44½ in. Crown to pubis = 24½ in. Pubis to ground = 20½ in. Upper : lower ratio = 1.2 : 1.

Dimensions approximately those of an average 6-year-old child.

Wide epicanthic folds. Lateral webbing of neck formed by folds of skin and subcutaneous tissue (Fig. 1). Low occipital hairline, with extension of hair growing in upward direction down sides of neck (Fig. 2). Pectus excavatus. Very mild right pes cavus. Cord-like superficial leg veins which were normally patent.



FIG. 1.—Turner's syndrome, showing facies and webbing of neck.

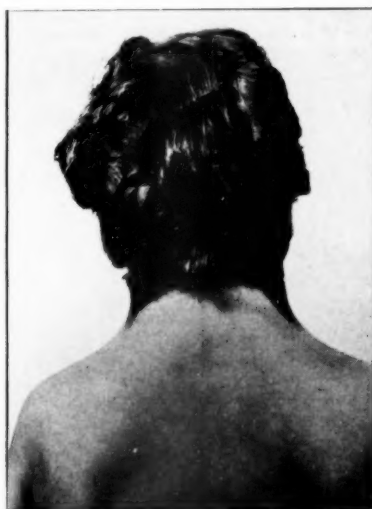


FIG. 2.—Showing the unusual hair line.

Cardiovascular system.—Excessive visible suprasternal pulsation. Radial pulses equal. Femoral pulses only faintly palpable. Posterior tibial and dorsalis pedis pulses not palpable. Systolic thrill in suprasternal region. Soft systolic murmur, maximal over 2nd right intercostal space and audible posteriorly. Scapular arteries palpable.

Blood pressure: Right arm = 155/115 mm. Hg. Left arm = 150/110 mm. Hg. Legs, undetermined.

Investigations.—*X-rays:* Chest 31.3.47: No rib notching. Chest 3.10.52: Slight notching of 5th and 6th ribs. Cervical spine: Spines of C5 and upper cervical region, ununited. Skeletal age: Consistent with chronological age.

ECG: Early evidence of left ventricular hypertrophy shown from chest leads.

Follicle-stimulating hormone excretion: less than 6 mouse units in twenty-four hours.

Discussion.—The patients described by Turner (1938) were all over the age of normal puberty and had four features in common: sexual infantilism, short stature, webbing of the neck and cubitus valgus. From other reports of similar cases it is clear that congenital abnormalities of the skeletal and cardiovascular system (especially coarctation of the aorta) are often included (Albright *et al.*, 1942).

Strictly, therefore, the use of the term "Turner's syndrome" in describing this case is incorrect, for cubitus valgus is missing and the patient is too young to show sexual infantilism. Probably, however, she will fail to develop the signs of puberty at the normal time because it is likely that she has primary ovarian agenesis in addition to the other congenital abnormalities.

The absence of an abnormally high urinary excretion of follicle-stimulating hormone does not invalidate the diagnosis at this age, but it is expected to begin to rise at about the age of 12 or 13 years.

Webbing of the neck may occur alone, as may cubitus valgus. Many cases of ovarian agenesis causing sexual infantilism have been reported without the rest of the congenital defects, even without the dwarfism. Nevertheless, it is useful to remember the existence of Turner's syndrome if only because the obvious physical deformity may lead to the uncovering of less obvious cardiovascular and endocrine defects, as it did in this case.

The syndrome is probably a collection of genetically determined anomalies due to developmental arrest in early foetal life. In cases of ovarian agenesis, laparotomy has usually revealed an infantile uterus with a thin streak of primitive ovarian tissue along the broad ligaments, consisting microscopically of a stroma of spindle cells without follicles.

Treatment.—Surgical treatment for the coarctation has been advised because of the height of the blood pressure and the patient being at the optimal age. Since hypertension of unknown causation may occur in patients with ovarian agenesis in the absence of coarctation, it is possible that surgical relief of the coarctation in this case may result in incomplete cure.

The webbing of the neck may be treated by plastic surgery if it is sufficiently unsightly. A Z-shaped incision, with reversal of the skin flaps so formed, lengthens the covering of skin at the side of the neck and corrects the deformity.

The sexual infantilism, foretold in this case, can be treated by administration of stilboestrol at the age of 14 years, and an imitation of menstruation can be achieved by withdrawing it at intervals.

The failure to grow presents a more difficult problem, because it is not due to any known endocrine insufficiency. Oestrogens, if given at this age, might produce a short-lived spurt of growth but would be contra-indicated in view of the danger of early epiphyseal fusion and because of the undesirable changes of precocious puberty.

REFERENCES

- ALBRIGHT, F., SMITH, P. H., and FRASER, R. (1942) *Amer. J. med. Sci.*, **204**, 625.
TURNER, H. H. (1938) *Endocrinology*, **23**, 566.
WILKINS, L., and FLEISCHMANN, W. (1944) *J. clin. Endocrin.*, **4**, 357.



FIG.
showing
with no
from wh

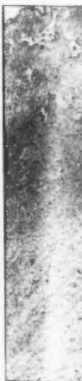


FIG. 2. —(A)
of epiphott
APRIE

Section of Epidemiology and Preventive Medicine

President—Professor ROBERT CRUICKSHANK, M.D., F.R.C.P., D.P.H.

[December 19, 1952]

Acute Epiglottitis (Acute Supraglottitis)

By FRANCIS E. CAMPS, M.D.

ON March 7, 1950, at Hendon, I carried out a post-mortem examination upon the body of a 5-year-old boy, which showed the epiglottis to be grossly swollen with a brawny red appearance and without any obvious ulceration or involvement of the true vocal cords or tonsils (Fig. 1). It appeared therefore to be localized completely and there were no significant naked-eye changes in any of the organs. The history was as follows:

R. H., a male child, one of two children of a chartered accountant had been perfectly healthy on Sunday 5.3.50 when he got up at 8 a.m. Whilst having breakfast he complained of pain in the throat and back of the neck. The temperature was 103° F. and the family doctor was called and tentatively diagnosed scarlet fever. During the day the child refused solid food and only swallowed fluids and the doctor called no less than three times. At 11.30 p.m. the child had a convulsion and died.

The post-mortem findings were a surprise to the doctor who had not suspected laryngeal obstruction.

Bacteriological examination of swabs taken from the surface of the epiglottis grew no organism of any significance but the sections showed an acute inflammation of the epiglottis limited in the same way as seen in the naked-eye specimen (Fig. 2A and B). The only other organ showing anything of significance was the spleen which showed a great increase of polymorphs in the pulp.

This case was similar in every way to another upon which I had performed a post-mortem examination on February 14 (three weeks before) except that there had been some ulceration of the epiglottis.

M. B., a female aged 17 months, had three weeks previously had bronchitis. At 4 a.m. on February 12 she was noted to be feverish with distressed breathing. She was admitted to hospital at 11.45 a.m. *in extremis* being comatose with cyanotic pallor and lower rib recession.



FIG. 1.—Photograph of larynx showing typical swelling of epiglottis with normal tissue. Case 18 (C.S.) from which *H. influenzae* was isolated.

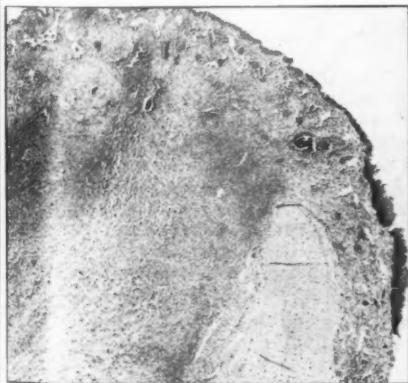


FIG. 2A.

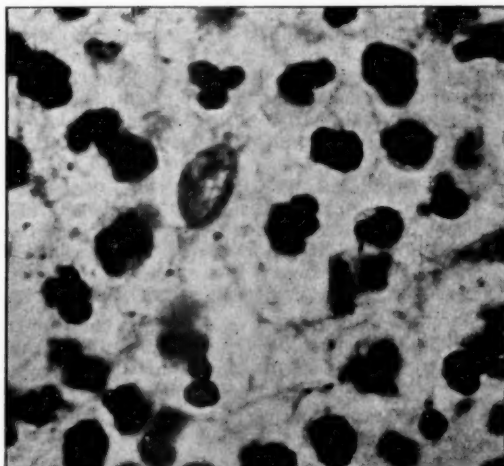


FIG. 2B.

FIG. 2. —(A) Section of epiglottis. $\times 18$. (B) Section of epiglottis showing micro-organisms. $\times 1,540$.

APRIL—EPIDEM. 1

She died suddenly at 1.45 p.m. having been restless just before death. The total length of the illness was nine and a half hours.

Post-mortem showed brawny red oedema of the epiglottis with ulceration but limited in its extent with no lesions in nasopharynx, trachea, or true vocal cords. Some patchy collapse of the lungs was noted with exudate into the bronchi.

Culture by the hospital laboratory gave a growth of *Str. viridans* only and the medical officer wrote to me asking whether this organism could account for the clinical condition. At this stage I thought it was probably a *Str. pyogenes* which had failed to grow owing to the lapse of time since death.

No further cases were seen until September 29, 1950, when a child died at Beckenham, Kent, with epiglottic oedema and some ulceration but again no involvement of the cords or tonsils.

M. W., aged 9 months, started to cry at midnight on September 29. At 9 a.m. he was seen by a doctor who prescribed penicillin medicine. During the afternoon the child's breathing became difficult and at 6.15 p.m. the doctor noticed laryngeal swelling and prescribed an inhalant. He died at 4 a.m. the next morning, a total illness of nineteen hours. Sections showed similar localized inflammatory process and bacteriology showed nothing significant.

In October 1950 another child died with a similar post-mortem picture but this time survived longer and hence more clinical observations were available.

B. A. S., a female aged 2½ years, gave a history of sudden onset of severe stridor six hours prior to admission to hospital. She breathed with difficulty and there was an expiratory stridor accompanied by severe intercostal recession. An X-ray revealed nothing but laryngoscopy showed gross oedema of the epiglottis and arytenoid cartilage which was red and inflamed. The white cell count showed a leucocytosis of 16,000 with excess of lymphocytes. An intratracheal tube was left *in situ* and she was given antidiphtheritic serum with penicillin 100,000 units three-hourly and placed in an oxygen tent. Aureomycin 0.125 gramme was also administered six-hourly but she died forty-eight hours after admission.

Culture grew alpha haemolytic streptococci and *N. catarrhalis* only.

Mr. Morus Jones, to whom I am indebted for the clinical notes, agreed with me that this was an example of laryngotracheobronchitis. During the next four months (1950-1951) I saw four more children who presented a similar clinical picture and post-mortem appearances. The bacteriology still yielded insignificant results.

There was a break during the summer but in the autumn (1951) two cases were seen with similar post-mortem appearances without any constant bacteriological findings. The possibility of a virus aetiology was considered but the histological appearances seemed to exclude it. Dr. J. C. Valentine suggested *Haemophilus influenzae* Type B as a possibility; this would fit in with the age-incidence. This explanation was encouraged by our seeing a child who had died of *Haemophilus meningitis* and who showed at autopsy slight swelling of the epiglottis which on section was due to an inflammatory reaction with round cells predominating. When two more cases were seen during the next six weeks, requests for bacteriological examination specifically mentioned *H. influenzae*. Although the material had been collected before death, the organism was not isolated. By this time I was so impressed by the age and seasonal incidence that I had some of the sections from earlier cases stained for organisms and at last I was able to discover what appeared to be cocco-bacilli.

Accordingly in the next case I seared the epiglottis and injected saline deep into the inflammatory area itself and from this the laboratory at Farnborough Hospital, Kent, isolated *Haemophilus influenzae* which was not typed. In the most recent case Dr. Valentine has isolated *Haemophilus* Type B both from surface culture and the deep tissues, which I believe to be the causative organism. Some additional bacteriological evidence was obtained from a case of Mr. Morus Jones' which recovered in December 1950. *H. influenzae* moderately sensitive to penicillin and sensitive to aureomycin was isolated from this case.

My records showed 4 apparently similar cases in 1944 (2), 1947 and 1949 respectively but I cannot recollect having seen one before 1944. All these had been called streptococcal infections but no positive bacteriological confirmation had been obtained, and experience of streptococcal nasopharyngeal infections gave me the impression that the clinical appearance and localized character did not seem quite right. Hence at a later stage they were labelled with the diagnosis of acute laryngotracheobronchitis although neither tracheitis nor bronchitis was present.

Clinical picture.—This series of cases seems to show a fairly clear-cut clinical picture of an acute localized infection of the epiglottis (probably due to *Haemophilus influenzae* Type B) causing respiratory obstruction showing the following features:

- (1) An age incidence of 9 months to 5½ years (Table I).
- (2) A seasonal incidence of autumn, winter and spring (Table III).
- (3) A clinical picture of
 - (a) Acute onset with pyrexia, sore throat, difficulty in swallowing and restlessness.
 - (b) No obvious nasopharyngitis.

TABLE
IN THE
English

Agas

0-1
1-2
2-3
3-4
4-5
5-6

(Female)

Rela
for on
due to
with o
condit

Exa
Type I
quotin
In c
could

Tabl
with th
and pe
culture
serum
isolation

All
treatm
where
appear
type B
indica
does n
sheck
as to
upon

Com
if the
(1)

(2)

(3)
exami
(4)
instu

- (c) Respiratory obstruction with expiratory stridor, grey-white cyanosis, rib-recession and swollen epiglottis.
- (d) *Sudden collapse* associated with acute laryngeal obstruction and rapid death, sometimes with terminal convulsions. This sudden deterioration was so rapid that, on several occasions, the doctor in attendance arrived to find his patient dead.

TABLE I.—AGE INCIDENCE
IN THE PRESENT SERIES

English Series	
Ages	Total
0-1	4
1-2	4
2-3	10
3-4	
4-5	
5-6	1
(Females 7, Males 12)	19

TABLE II.—AGE INCIDENCE OF AMERICAN SERIES

American Series		1941	1942	1943	1947	1948	Total
Ages		Sinclair	Alexander <i>et al.</i>	Du B., Aldrich	Davis	Miller	
0-1		1					1
1-2		1	3	2	2	1	9
2-3	}	3	5	2		7	17
3-4							
4-5		5	1		1		7
5-6							
		10	9	4	3	8	34

TABLE III.—SEASONAL INCIDENCE
Series

Jan.	Feb.	Mar.	Apl.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
2	4	2	—	1	—	—	—	2	1	3	4

Relevant literature.—The literature in this country gives no specific reference to the condition except for one case described by De Navasquez (1942) under the title of "Acute laryngitis and septicæmia due to *H. influenza* Type B". This differed from those of the present series being a generalized infection with œdema of the uvula and nasopharynx. However, it may possibly be a later stage of the same condition.

Examination of the American literature shows a similar clinical picture associated with *H. influenza* Type B to have been recognized as far back as 1941, when Sinclair (1941) described 10 cases, he himself quoting Le Mierre (1936).

In one respect there is a significant difference, the American mortality rate is much lower which could be explained by a failure in this country to diagnose the non-fatal cases.

Table II shows a table of age incidence of the various American writers which seems comparable with the present series. Far more investigation of the patient during life has been possible in America, and positive blood cultures have been frequently secured. The organism has been identified both by culture and by what is described as "quelling", demonstration of capsule swelling using type B rabbit serum, and material collected from the local lesion (Alexander *et al.*, 1942), or the organism after isolation by culture.

All the writers are fully alive to the severity of the condition and its rapid onset and recommend treatment which has been modified as new weapons against infection have been discovered. Thus, whereas originally the cases were treated with chemotherapy and penicillin, nowadays better results appear to have been obtained by the use of aureomycin or chloromycetin, penicillin and, on occasions, type B rabbit serum. The lesion being localized in the supraglottic region, tracheotomy is clearly indicated in many cases but it is stated that although the obstruction is relieved, clinical improvement does not occur for some forty-eight hours and there seems to be quite a disproportionate state of shock associated with the condition. This, however, may not be due so much to the infection itself as to the mechanically produced anoxia. Intubation is not recommended, involving as it does pressure upon grossly inflamed tissues.

Conclusions.—The study of this small series of fatal cases appears to warrant the following conclusions if the American disease is the same.

- (1) The existence in this country as well as in America of the clinical entity of acute epiglottitis due to *H. influenza* Type B.
- (2) There is strong evidence that, in fact, such cases have occurred since 1944 and are probably increasing, a similar experience to that of American observers.
- (3) Greater attention will have to be paid to the presence of *H. influenza* type B in the routine examination of throat swabs.
- (4) An appreciation of the existence of the condition may lead to earlier diagnosis and the institution of appropriate treatment, with consequent reduction in mortality.

Comments.—The solution of the problem which is of fundamental importance, would seem to lie in the explanation as to why at one stage of what is probably a blood-stream infection this latter should be so localized and to the epiglottis of all places. Table IV, based in part upon the American observations, shows the points of differential diagnosis between acute epiglottitis and acute laryngo-tracheobronchitis.

TABLE IV.—DIFFERENTIAL DIAGNOSIS WITH ACKNOWLEDGMENT TO NEFFSON (1949)

	Acute epiglottitis	Acute laryngotracheobronchitis
Age	1½–5	
Onset	Abrupt (1–5 hours)	Insidious up to 2 days
Course	Rapid and fulminating	Slower
Pyrexia	104°–106° F	102°–103° F
Restlessness ..	Present	Present
Voice	Muffled guttural	Hoarse
Throat	Sore—difficult to swallow	Not sore
Breathing early ..	Low-pitched inspiratory stridor	Early croaking stridor. Later high-pitched stridor.
	Louder low-pitched coarse expiratory rattle (snore)	
Breathing later ..	High-pitched inspiratory stridor or no inspiratory stridor, expiratory stridor unchanged (Dry sounds)	
	Wet sounds are due to mucus	
Position	No rales	Rales present
Toxæmia ? Shock ..	Sitting up	Lying down
Epiglottis	Severe	Nil
Bacteriology ..	Grossly swollen characteristic	Normal
	<i>H. influenzae</i> Type B: blood and epiglottis	Usually no <i>H. influenzae</i> type B. Various organisms
Diagnosis	<i>Direct laryngoscopy</i>	
	Shows swelling	No change
Treatment	Antibiotics	Antibiotics
	Tracheotomy	Tracheotomy may not be indicated
	Type-specific serum	Cool steaming

My thanks are due to H.M. Coroners of the various districts for their assistance and to those of my colleagues who have helped me and especially to Mr. Derek Martin of the Hospital for Sick Children, Great Ormond Street.

BIBLIOGRAPHY

- LE MIERRE, A., MEYER, A., and LAPLANE, R. (1936) *Ann. Méd.*, **39**, 97.
 SINCLAIR, S. E. (1941) *J. Amer. med. Ass.*, **117**, Pt. 1, 170.
 ALEXANDER, H. E., ELLIS, C., and LEIDY, G. (1942) *J. Pediat.*, **20**, 673.
 DE NAVASQUEZ, S. (1942) *Brit. med. J.*, ii, 187.
 DU BOIS, P. G., and ALDRICH, C. A. (1943) *J. Pediat.*, **23**, 184.
 STEIGLER, C. (1946) *Clin. Proc. Child. Hosp. Wash.*, **2**, 185.
 DAVIS, H. V. (1947) *J. Kans. med. Soc.*, **48**, 105.
 MILLER, A. H. (1948) *Laryngoscope*, **58**, 514.
 RABE, F. E. (1948) *Pediatrics*, Springfield, **2**, 559.
 NEFFSON, A. H. (1949) Acute laryngotracheobronchitis, New York.

Section of Dermatology

President—G. B. DOWLING, M.D., F.R.C.P.

[October 16, 1952]

Case for Diagnosis. ? White Sponge Nævus of the Mouth.—R. P. WARIN, M.D., M.R.C.P.

E. P. S., male, aged 24.

History.—Condition first noticed at about 5th year of age. It never cleared but improved on one occasion when fasting during an "influenza" attack. Worse after spiced or acid foods.

Family history.—One brother aged 21. No similar condition in the family.

On examination.—White, macerated appearance of the inner aspects of the lips, dorsum and sides of the tongue, hard palate, and over the cheeks opposite the line of closure of the teeth. The superficial layers of the white membrane can easily be scraped off but the deeper layers separate with difficulty and leave a raw, bleeding surface.

Investigations.—Blood W.R. and Kahn negative. Scrapings showed no monilia present. Biopsy: Hyperkeratosis and parakeratosis present. Moderate infiltration of the dermis with neutrophil and lymphocytic leucocytes.

Therapy.—A course of vitamin A in high doses for two months had no effect.

Comment.—Chronic moniliasis is difficult to disprove in spite of negative scrapings. However, the condition seems to be very similar to that described by Cannon (1935) as "White sponge nævus of the mouth." However, his case also had lesions in the vagina and rectum and had a well marked family tendency. Ludy and Shirazy (1941) described another case under the title "Leukokeratosis mucosa oris", and in this case, too, there was a family tendency.

POSTSCRIPT (31.3.53).—A lung X-ray was carried out and showed no abnormality present.—R. P. W.

REFERENCES

- CANNON, A. B. (1935) *Arch. Derm. Syph., Chicago*, **31**, 365.
LUDY, J. B., and SHIRAZY, E. (1941) *New Int. Clin.*, **4**, 39.

Dr. M. Sydney Thomson: It seems to me it must be nævoid; in fact the curious patches running in streaks reminded me of ichthyosis hystrix which behaves as this mouth lesion behaved in regard to its gradual spread and variation in intensity.

Dr. H. J. Wallace: I suggest further repeated examination for monilia.

Dr. J. E. M. Wigley: Has a monilial infection of the lung been excluded or an X-ray taken? Dr. H. G. Oliver in Jersey has found a considerable number of cases in which a moniliasis of the external surface seems to have been kept going by a moniliasis of the lung. It commences in quite young patients.

Dr. R. P. Warin: A lung X-ray has not been taken but we will have it done. He has had the condition for twenty-one years and there have been no symptoms of lung infection. Even if monilia are demonstrated it would not necessarily indicate that they were playing a primary role since if the condition were fundamentally nævoid it would be the sort of field on which monilia like to grow.

Poikiloderma Congenitale (Thomson).—C. H. WHITTLE, M.D.

H. D. G., girl aged 3 years.

History.—Pin-head vesicles and some patchy erythema came on the face and hands at 2 days old. Sunlight appeared to bring out the rash which cleared in the winter. The vesicles have ceased. The child was 5½ lb. at birth and has never developed properly.

10.11.50: When first seen the face showed a red mottled pattern on the cheeks suggestive of poikiloderma and some erythematous patches on the dorsa of the hands.

APRIL—DERMAT. I

Family history.—Father had infantile eczema. Mother's sister suffers from asthma. Two brothers aged 3½ years and 9 months are normal.

Present condition.—There is a vermillion reticulate pattern of telangiectasia on the cheeks with a faint suggestion of "glazing" and an occasional scaly or horny patch. The hands and shins show fading patches of erythema. The mother states that sun does not now seem to affect the skin. The child is still microcephalic, grossly undersized and mentally backward. There are no gross keratoses. The shape of the face is somewhat triangular with the apex at the chin.

Blood vitamin A.—22.6.51: Carotenoids 116 i.u./100 ml. Vitamin A 75 i.u./100 ml. 1.10.52: Carotenoids 111 i.u./100 ml. Vitamin A 65 i.u./100 ml.

Comment.—It is interesting to note that two of Thomson's original (1936) cases showed microcephaly and one was "small and puny" from birth. These features were also noted by Rook and Whimster (1949) in their review of Dowling's case (1931). Other dystrophies occur such as bilateral cataracts and dental defects. Mild xeroderma was noted by Thomson in one case and by Rook and Whimster in theirs. Mild xeroderma was present in the second of two cases published by me (1947). The blood vitamin A was low in both my patients, 45 i.u. and 65 i.u./100 ml. in one, 85 i.u. in the other, as compared with 75 i.u. and 65 i.u. in this case. The syndrome would therefore appear to include the tendency to other maldevelopments and possibly a disturbance of vitamin A metabolism associated with the characteristic dyskeratosis.

REFERENCES

- DOWLING, G. B. (1931) *Proc. R. Soc. Med.*, **24**, 1648; *Brit. J. Derm.*, **43**, 598.
 ROOK, A. J., and WHIMSTER, I. (1949) *Brit. J. Derm.*, **61**, 197.
 THOMSON, M. S. (1923) *Brit. J. Derm.*, **35**, 455.
 — (1936) *Proc. R. Soc. Med.*, **29**, 453; *Brit. J. Derm.*, **48**, 221.
 WHITTLE, C. H. (1947) *Proc. R. Soc. Med.*, **40**, 499; *Brit. J. Derm.*, **59**, 381.

Dr. M. Sydney Thomson: I think this is a typical example of the condition. A point which has always impressed me is the disproportion in the ossification of the cartilage and membranous bones of the skull.

The President: A case under my care, when I first saw her at the age of about 20, presented the vascular change in the face seen in Dr. Whittle's case, a scaly xeroderma-like alteration of the skin of the arms and legs, the characteristic small skull and features, as well as a large number of keratoses situated chiefly on the forearms and legs. Histological examination of these keratoses at that time revealed no sign of malignancy. However, some years later she developed a large epithelioma on the right ankle and this eventually led to amputation of the limb. Since then others have developed malignant change and recently metastases have occurred in regional glands. This seems to be the probable fate of at least some of these cases in adult life. The case has been fully reported by Rook and Whimster.

Dr. C. H. Whittle: I should like reassurance that these vitamin-A figures are below normal. The normal standard seems to vary so much between one country and another and from year to year.

Dr. A. D. Porter: They are certainly lower than the ordinary figures for England. Leitner, Z. A., and Moore, T. (1946, *Lancet*, ii, 262) found the average figure in hospital out-patients suffering from common diseases of the skin to be 120 i.u./ml. Less than 80 i.u./100 ml. is certainly low.

Miliary Lymphocytoma of the Face.—E. WADDINGTON, M.D., M.R.C.P.

Mrs. M. K., aged 42.

History.—July 1951 the eruption began suddenly on the lateral aspects of both cheeks and new lesions have gradually developed on the malar regions and forehead. The condition remained unchanged until a month ago when some of the spots on her forehead disappeared spontaneously.

She lived in New Zealand and Australia until eighteen months ago and has always spent considerable time in the open air. The eruption occurred after she had been in this country for two months; she does not think it followed sunburn.

Previous history.—1941: Dengue fever. May 1952: Operation for removal of lutein cyst of the ovary.

On examination.—There is a symmetrical eruption on the forehead, malar regions and pre-auricular areas of the cheeks extending downwards towards the chin. The lesions are discrete papules varying in size from a pinhead to 3 mm. in diameter. The larger lesions are reddish-brown in colour, the smaller are semi-translucent and resemble sago grains. All the lesions show opalescence on diascopy. There is no scaling. The rest of the skin and mucous membranes are not involved.

Reticulo-endothelial system: There is no lymphadenopathy and the liver and spleen are not palpable.

Investigations.—Blood count normal.

Biopsy report (Dr. I. W. Whimster).—The section shows parts of three sharply circumscribed, discrete, dermal nodules of tightly packed, fairly evenly mixed large and small reticulum cells, "lymphoblasts" and lymphocytes, together with an occasional eosinophil. The appearances are those of a "benign light-sensitive lymphoma".

Comment.—This condition was first described by Jadassohn in 1906 under the title of pseudo-leukæmic infiltration of the skin; but in 1921 he reported that his patient never developed signs of leukæmia, although the lesions had been present for thirty years.

The name lymphocytoma was first used in 1921 by Kaufmann-Wolf and similar lesions have been recorded under diagnoses such as localized Spiegler-Fendit sarcoid, lymphadenosis benigna cutis and benign lymphadenoid granuloma.

There is considerable difference of opinion about the ætiology.

In Europe it is regarded as a benign reaction of lymphoid tissue in response to various stimuli. In 1939 Hallam and Vickers and in 1943 Bafverstedt came to the conclusion that in all proved cases malignant degeneration never occurred.

At the International Congress in 1952 Bafverstedt produced evidence that it may occur as a symptom of malignancy elsewhere in the body. He reported 3 cases in association with carcinoma of the œsophagus, a squamous-cell epithelioma of the skin, and dermatofibrosarcoma protuberans.

On the other hand, American authors are not yet decided that it is entirely benign, and this difference of opinion arises from the difficulty in interpreting the histological changes. Two types are described. In one, the infiltrate forms discrete nodules, and in the other, it is diffuse. Both types may, or may not, show the formation of germ-centres and Loveman and Fliegelmann (1951) point out that it is sometimes impossible to distinguish the diffuse type without germ-centres from a malignant lymphoma.

Although a final decision can only be made after prolonged follow-up of all cases, the evidence at present is more in favour of the belief that miliary lymphocytoma is a benign reactive hyperplasia of pre-existing lymphoid tissue. This peculiar reaction occurs in response to irritation of the skin by such varied stimuli as sunlight, minor trauma and even insect bites.

REFERENCES

- BAFVERSTEDT, B. O. (1943) *Acta derm.-venereol., Stockh.*, (Suppl. 11), 24, 1.
 — (1952) *Excerpta med., Amst.*, 6, Section XIII, 352.
 HALLAM, R., and VICKERS, H. R. (1939) *Brit. J. Derm.*, 51, 251.
 JADASSOHN, J. (1906) *Arch. Derm. Syph. Wien.*, 82, 297.
 KAUFMANN-WOLF, M. (1921) *Arch. Derm. Syph. Wien.*, 130, 425.
 LOVEMAN, A. B., and FLIEGELMANN, M. T. (1951) *Arch. Derm. Syph., Chicago*, 63, 169.

Dr. I. W. Whimster: The name "lymphocytoma" seems to be used to describe lesions of apparently different nature.

The cases we have had at St. Thomas's which belong in the broad category of "lymphocytoma" fall into two distinct groups, both on their histology and on their natural history.

In the first group are lesions such as those in Dr. Waddington's patient. Histologically they consist of almost spherical nodules of an even mixture of cells of the reticuloendothelial series, ranging from large reticulum cells down to lymphocytes and including many eosinophils and small giant cells. The blood vessels in the infiltrated area show gross enlargement of their endothelial nuclei and give the impression that they may be the origin of the free reticulum cells and the small giant cells.

We have examined material from 5 such cases so far and in each one the conspicuous features are the even mixture of the cells and the lack of organization into germinal follicles. These 5 cases in addition to having a similar histology have closely resembled each other clinically. The lesions have in each case been multiple (ranging from 4 or 5 to hundreds), small (up to 1 cm. diameter), confined to exposed surfaces and all have been sensitive to light—swelling and itching on exposure to strong sun. So far none of these cases has shown involvement of tissues other than exposed skin. 2 cases have been followed for twenty and twelve years respectively but longer follow-up on more cases will be required before this state can be confidently labelled benign. From its behaviour it would seem likely that it is to some extent the result of exposure to light.

The second type of lesion is that which we call follicular lymphoma. The histology of these consists of multiple discrete and confluent, fairly sharply margined accumulations of lymphocytes in the centre of which are to be found germinal centres of large reticulum cells. The structure of such lesions appears to be identical with the lymphoid tissue which develops in the dermis sometimes in lupus erythematosus, primary atrophy of the vulva and other chronic inflammatory states. In follicular lymphoma, however, the presence of the lymphoid tissue is unaccompanied by other changes in the skin.

Clinically the lesions of follicular lymphoma differ from those of the first group in growing to a larger size (up to an inch or more in diameter), in not confining themselves to exposed sites and, when they do affect such sites, in not being light-sensitive. In addition, the skin deposits of follicular lymphoma are frequently accompanied by glandular ones and both appear able by a process of gradual transition to become one of the malignant lymphomas, reticulum-cell sarcoma, Hodgkin's disease and so on.

The President asked whether there was any known way of dealing with the cases.

Dr. H. R. Vickers: Dr. Rupert Hallam and I described 2 cases in 1939 (*Brit. J. Derm.*, 51, 251) and both these cases responded well to superficial X-ray therapy, 3 exposures of 133 r at fortnightly intervals.

Dr. M. Sydney Thomson: It might be helpful to undertake further study of the foetal skin in this connexion, for we must not forget the embryological functions of that tissue. It may be possible to distinguish then between these two groups.

The following cases were also shown:

Case for Diagnosis. ? Malignant Granuloma.—Dr. D. E. OAKLEY.

Multiple Naevoid Basal-cell Epitheliomata. ? Porokeratosis of Mantoux (Two Cases).—Dr. C. D. CALNAN.

Erythema Chronicum Migrans (Lipschütz).—Dr. STEPHEN GOLD.

Lichenoid Gold Eruption.—Dr. R. H. MEARA for Dr. G. B. DOWLING.

Disseminated Granuloma Annulare, Showing Necrobiosis Maculosa (Miescher).—Dr. I. S. HODGSON-JONES.

Ectodermal Dysplasia with Universal Pili Torti: Retinitis Pigmentosa.—Dr. D. S. WILKINSON.

Squamous-cell Epithelioma.—Dr. D. S. ANDERSON and Dr. R. H. SEVILLE.

Pachonychia.—Dr. B. SCHWARTZ.

Lichen Sclerosus et Atrophicus of Trunk and Penis (? Early Balanitis Xerotica Obliterans).—Dr. BRIAN RUSSELL.

(These cases may be published later in the *British Journal of Dermatology*.)

[November 20, 1952]

Dermatomyositis.—J. R. SIMPSON, M.R.C.P.

Mrs. E. B., aged 52.

History.—Left local mastectomy was performed in 1943 for "a lump in the breast". In 1948 she noticed irritation in that area.

When seen in October 1949 the tissues beneath and around the scar were indurated and there were two raised firm nodules in the area. Histological examination of a nodule showed scirrhous carcinoma. She was transferred to the Plastic Surgery Unit at Frenchay, Bristol, under the care of Mr. G. M. FitzGibbon.

Operation (December 6, 1949).—The skin and underlying tissues in the left pectoral area were excised, together with the anterior ends of the second and third ribs, and the left axilla was cleared. The wound was closed by a pedicle flap from the abdomen, carried up on the left forearm. A small marginal loss along the upper edge of the flap was afterwards covered with a Thiersch graft. The histological report indicated that the growth had extended below the deep surface of removal.

Her condition was satisfactory until May 1952. She then developed redness and swelling of the eyelids and face. The swelling subsided in a month but the redness persisted and was later accompanied by scaling. These changes have gradually extended to the scalp, neck, right pectoral area, the shoulders and upper limbs and, most recently, the fronts of the knees. Itching has been a marked feature throughout. There has been no loss of hair. During this period there has been a gradual loss of muscle power. She has also developed slowness in speech and slight dysphagia.

On examination.—There is erythema and fine scaling on the scalp, pinnæ, all round the neck, the eyelids and on the face. On the right side the rash extends over the shoulders and below the clavicle to the level of the second rib. On the left side it stops abruptly at the upper edge of the graft, just below the clavicle. The whole of the upper limbs is affected, except the medial aspect of the arms and the palms. Below the elbows and on the patches over the front of the knees there is conspicuous hyperkeratosis which shows a discrete follicular pattern in many areas, but is confluent in others. This change is well shown over the knuckles and the interphalangeal joints.

Muscular weakness is shown in the grip and in her inability to sit up from the supine position. Muscle wasting is not very marked, except in the interossei and sclerosis is not obvious.

The pectoral graft is healthy except for a small crusted ulcer at the upper edge. There is a hard subcutaneous nodule in the left axilla, presumably a lymph gland.

Investigations (since November 6, 1952).—Skiagrams of chest, skull, dorsal and lumbar vertebrae show no evidence of metastases. X-ray shows normal movement of the diaphragm; heart and aorta normal in size and shape; cesophagus normal. Blood count normal. E.S.R. 19 mm. in one hour (Wintrobe). Creatine excreted in twenty-four hours = 0.083 gramme. Creatinine excreted in twenty-four hours = 0.59 gramme.

Plasma proteins: Total 8.95; Albumin 3.90; Globulin 5.05 grammes %. Albumin-globulin ratio = 0.78 : 1.0.

W.R. negative. ECG normal.

Histology (Dr. G. Stewart-Smith).—Skin of right forearm and brachioradialis muscle:

Skin: The epidermis shows slight hyperkeratosis with patchy stretching of the malpighian layer and loss of papillae. At the lower margin of the epidermis there are many dilated lymph channels and some small capillaries, and around these a moderate number of small round cells and some histiocytes: there is some oedema of the deeper layer.

Immediately beneath the epidermis the connective tissue has a sclerodermatous appearance and deep to this the collagen is rather coarse but does not show any "caking" such as was described by Dowling and Freudenthal (1938).

Thionin stain failed to demonstrate mucin.

Muscle normal.

POSTSCRIPT.—She received ACTH intravenously, 25 mg. daily for a week, during which time the eruption faded and muscular power increased. Treatment was stopped abruptly on account of an acute bronchopneumonia from which she made a rapid and complete recovery. In spite of this her dermatomyositis continued to improve and two weeks after the last dose of ACTH the skin showed only faint brown staining and scarcely any hyperkeratosis; she could rise, unaided, direct from the supine position and her grip had doubled in power, as measured by a dynamometer.

REFERENCE

DOWLING, G. B., and FREUDENTHAL, W. (1938) *Brit. J. Derm.*, **50**, 519.

Dr. L. Forman: This patient was operated on some time ago for an ovarian disorder and a uterine polypus was removed, the exact pathology of which has, unfortunately, not been determined.

The hyperkeratotic erythema shown in this case recalls the similar areas demonstrated in a patient in whom the diagnosis of "query" lupus erythematosus had been offered. This patient, a young man, subsequently died of carcinoma of the colon (*Proc. R. Soc. Med.*, 1938, **31**, 474).

In these cases of dermatomyositis occurring in late middle age there would appear to be in many cases an associated visceral carcinoma.

Onchocerciasis.—K. D. CROW, M.R.C.P., and R. H. SEVILLE, M.D.

N. C., male, aged 27.

History.—Over three months ago, a few weeks before returning to England, an intensely irritating papular eruption appeared on the patient's back and, later, on the outer sides of his buttocks. This has remained essentially unchanged since then, except that individual lesions wax and wane in prominence, although none has actually disappeared. He has also noticed that the papules are more prominent and more irritating when his skin is warm.

For the past two years, the patient has been engaged in agricultural research projects in the Gold Coast territory of West Africa. During most of this time, his work has taken him into the interior where he has been forced to live under somewhat primitive conditions.

On examination.—Across the shoulders and tapering off down to the lumbar region is an area in which are numerous, flesh coloured, rounded papules about $\frac{1}{8}$ in. in diameter (Fig. 1). Many of these have been excoriated. On the outer sides of the buttocks are other papules, slightly larger and seeming deeper than those on the back. There are no excoriations in these areas. No firm subcutaneous nodules could be palpated. General examination of other systems reveals no abnormalities.

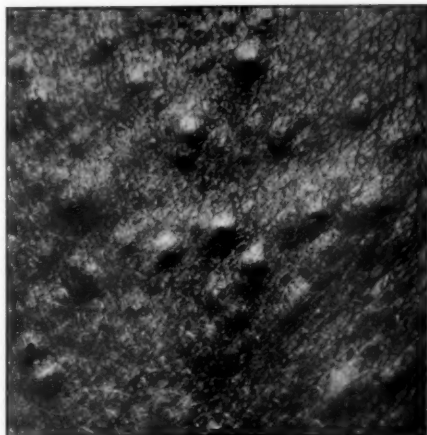


FIG. 1.—Onchocerciasis showing typical papular lesions on upper part of the back.

Special investigations.—Skin shavings: No embryos found. White cell count: 47% eosinophilia. Day and night blood films: No microfilaria seen. Faeces: No pathogenic ova or protozoa found. Filarial skin test positive; filarial complement-fixation test (C.F.T.) negative (performed at the Hospital for Tropical Diseases).

Histological section (papule).—Non-specific, perivascular eosinophilic and round-cell infiltration.

Special report (Dr. W. H. Jopling, Hospital for Tropical Diseases (U.C.H.)).—"The skin changes are typical of onchocerciasis. Firm, mobile subcutaneous nodules are usually found later in the course of the disease, and are especially to be looked for in the region of the iliac crests. They contain the coiled-up female worm. Such nodules are not present in this patient. The results of the special investigations carried out at St. John's Hospital have been confirmed, and skin test and complement-fixation test carried out as recorded above.

One frequently finds difficulties in demonstrating embryos of *O. volvulus* in skin shavings, and warming the skin sometimes helps. Also, the blood films are always and the C.F.T. may be negative in proved cases. The skin test and the C.F.T. are group tests for the filaria worms and are not specific for onchocerciasis. Infections with *Loa loa* and *Acanthocheilonema perstans* are excluded by the negative day-blood films and *W. bancrofti* by the negative night-blood films. Note that the skin test will remain positive for the rest of the patient's life, but the C.F.T. becomes negative a few months after the infection has been eradicated.

Treatment is being commenced with Banocide (Hetrazan) and dosage will gradually be increased from $\frac{1}{2}$ mg./kg. t.d.s. to a maximum of 3 mg./kg. t.d.s. The whole course should take three weeks or more. The initial dose is being made less than the usual commencing dose of 1 mg./kg. t.d.s. in view of the fact that we suspect early eye involvement, judging by the patient's complaint of photophobia. Early in the course of treatment, an allergic reaction is not unlikely, and a small commencing dose is advisable in patients with eye involvement, in view of the potential hazard of an allergic reaction in the eyes. Should such a reaction occur, cortisone will be administered."

Acknowledgment.—We would like to thank Dr. G. B. Dowling and Sir George McRobert for permission to show this case.

The President: Dr. Seville was responsible in the first place for the diagnosis of craw-craw. That apparently is a generic term which covers any eruption caused by filaria. The question was which one was responsible in this case. Onchocerciasis was suggested and seems likely to prove the correct diagnosis.

Dr. L. Forman: Is this an allergic reaction, and are there microfilariae in the skin?

Dr. Seville: Though difficult to demonstrate, microfilariae are found in the lesions and occasionally in otherwise normal skin; I cannot say whether the local reaction always depends on their presence, but I would expect it to be the case. The lesions start as an itching papule which may become vesicular, then excoriated and finally pruriginous. In the late stages, small cratered scars remain showing particularly well on pigmented skin.

Dr. J. Sommerville: We have had 2 cases in the Glasgow area, both from West Africa, presenting a very similar picture. The picture which I have seen could be described loosely as not unlike the picture Dr. Seville has given. It seems to come out mainly on the trunk and limbs and it gives an indeterminate follicular papular arrangement with a little scarring. There was very marked eosinophilia. It could be very confusing until one went into the question of where these people had been. It was treated with Hetrazan, with good results.

POSTSCRIPT.—After a week of treatment with Banocide, a considerable allergic reaction of the Herxheimer type occurred. The patient's photophobia increased and many more papules appeared on the back and irritation became much more severe. After two weeks of Banocide, the full dosage of 3 mg./kg. was reached and was continued for a further three weeks, the whole course taking five weeks in all. At the end of this time, all the skin lesions had disappeared and the photophobia was no longer present.

As to the prognosis: Banocide does not kill the adult worms but only the microfilariae; so that it must be anticipated that the patient will get further lesions. He must be kept under periodic observation, therefore, and treated with Banocide again, if and when necessary.

The ultimate outlook, however, is quite good.—K. D. CROW.

The following cases were also shown:

Erythema Elevatum Diutinum.—Dr. R. M. B. MacKENNA, Dr. K. D. CROW and Dr. H. HABER.

Dermatitis Herpetiformis and Arsenical Pigmentation Treated by Hypnosis.—Dr. K. H. COHEN.

Multiple Leiomyomata.—Dr. G. A. BECK for Dr. H. T. CALVERT.

Microsporon Scalp Ringworm in an Adult.—Dr. C. H. WHITTLE.

Two Cases of Granulomatosis Disciformis Chronica et Progressiva (Miescher).—Dr. C. D. CALNAN.

Necrobiosis Lipoidica Diabeticorum.—Dr. D. L. REES for Dr. G. B. DOWLING.

Erythema Gyratum Perstans.—Dr. A. D. PORTER.

Skin Reaction to Sea Urchins.—Dr. P. R. MONTGOMERY for Dr. E. J. MOYNAHAN.

Nævus Syringo Cystadenoma Papilliferum.—Dr. H. BLACK, for Dr. G. B. MITCHELL-HEGGS.

Lichen Planus.—Psoriasis.—Dr. B. SCHWARTZ.

(These cases may be published later in the *British Journal of Dermatology*)

Section of Endocrinology

President—S. LEONARD SIMPSON, M.A., M.D., F.R.C.P.

[October 22, 1952]

DISCUSSION ON THE PHYSIOLOGY AND CLINICAL DISORDERS OF THE PARATHYROID GLANDS

Dr. C. E. Dent:

Physiology of the Parathyroid Glands

I will not discuss here the factors which influence the production from the gland of parathyroid hormone, or parathormone. Suffice it to say that the evidence for participation of the pituitary is fragmentary and is at least of no clinical importance. The function of the parathyroid gland is, however, closely concerned with the blood calcium level, both its size and its hormone production being increased when the blood calcium is low and decreased when it is high. These facts seem to be beyond dispute. The evidence that it is also influenced (in the opposite sense) by the blood phosphate level is at the moment ambiguous.

The nature of the peripheral action of parathormone has attracted a great deal of attention, since this is closely concerned with a clinical matter of interest and importance, namely, the very difficult but rewarding problem of making a firm diagnosis of hyperparathyroidism. It is with this that I will concern myself. I will mention first the two main theories concerned with the alleged primary action of parathormone and then produce some destructive criticism of one. I will end with a description of a compromise scheme.

The first theory was proposed by Collip *et al.* (1925) who based their views on the histological findings in the bone in cases of hyperparathyroidism. They believed simply that the primary action of parathormone was on bone, that it caused a stimulation and multiplication of osteoclasts, and that the ensuing resorption of bone liberated the contained calcium and phosphorus (as phosphate) into the circulation. The ensuing changes in blood electrolyte levels were all supposed to be secondary to the bone changes. This theory explains well the raised blood calcium levels which are so characteristic of the disease, and the tendency to ectopic calcification, due presumably to oversaturation of body fluids with calcium phosphate. It does not explain the low blood phosphate levels that are always found in hyperparathyroidism in the absence of secondary renal disease.

Albright and Reifenstein (1948) have been the main supporters recently of the alternative theory that the primary action was on the kidney and that any action on bone was of less importance. It is easier to understand this viewpoint if it is seen against the background of Albright's main clinical contribution in this field. This is the fact he has so repeatedly stressed that hyperparathyroidism, although originally described as a severe disease of bone, could also occur in the absence of any demonstrable bone changes. Indeed these cases, which usually presented with renal damage or stones, were much commoner than the others. The diagnosis had then to be made purely by biochemical means; determinations of blood levels, urinary excretion and so forth. Clearly the important part played by the kidney in such circumstances would have to be emphasized.

Albright has attached a great deal of importance to the findings of Ellsworth and Howard (1934), which he subsequently confirmed and extended, on the immediate changes taking place in blood and urine after a single intravenous injection of 200 USP units of parathyroid extract. These findings were that there was at once an increased excretion of phosphate, followed by a fall in serum phosphate. This could only be interpreted as an increased clearance of phosphate by the kidney. The rises in serum and urine calcium levels only followed after some hours, and were therefore considered to be the result of the changes in phosphate levels. This is the weak point of the argument since Albright could only attempt this correlation by invoking the mysterious, but undoubtedly real, calcium-phosphorus product mechanism. He argued that this mechanism was stimulated by the fall in serum phosphate and that the bone was dissolved in order to provide the extra calcium required to raise the blood level in the expected compensatory fashion. Once this hurdle was crossed the rest was straightforward enough. The raised serum calcium produced a large urinary excretion and its maintenance necessitated continuous bone dissolution. Whether or not the patient got frank osteitis fibrosa depended on whether his calcium intake was adequate to compensate for the large continued loss in the urine. Note here that Albright, unlike anybody else, has made a serious attempt to explain the fact that hyperparathyroidism may or may not be associated with demonstrable bone disease.

The essential features of his scheme are summarized diagrammatically in Fig. 1. Note that it comprises a chain of events following each other, and that if one link of the chain is broken the whole scheme must fall to the ground.

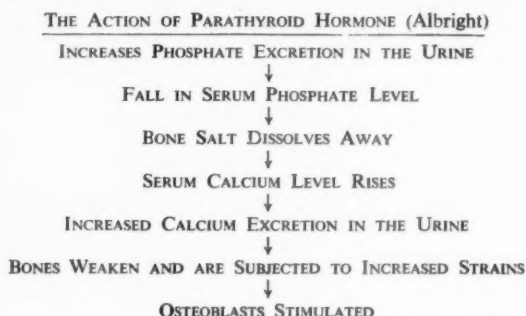


FIG. 1.—The sequence of events following an injection of parathyroid hormone—according to Albright.

I will now mention some unpublished work with my collaborators Dr. A. D. Kenny and Mr. G. Philpot, in which we have repeated the parathormone test of Ellsworth and Howard. We have used several batches of the hormone from the two U.S. manufacturers, Eli Lilly and Parke Davis. We had two good opportunities to confirm that their hormone was active in raising the plasma calcium level in patients with post-operative hypoparathyroidism. In 20 tests on 10 subjects (mostly normals) however, the hormone produced hardly any increase in phosphate excretion. The effect was slight if present at all. Our results closely paralleled those of Milne (1951). One hypoparathyroid patient likewise showed no effect, two others showed about threefold increases only. The plasma changes were interesting. There was an almost invariable slight rise in calcium level, thus confirming the activity of the hormone preparation. The phosphate level, however, only fell convincingly when it was already high to begin with; when it was normal, the changes were variable and insignificant. Our conclusions from this work are as follows: Firstly, the phosphate excretion effect of parathormone is insignificant in the modern preparations used of active hormone assayed as usual on the basis of its calcium raising power. Secondly, its variability in action in our hands as compared with the results of others suggests that the phosphate excretion effect when present is due to a different factor from that responsible for calcium raising. This could either be an artefact or the real action of a second parathyroid hormone. Finally, whatever the explanation of our results we believe that they weaken the Albright theory which has been so firmly based on the Ellsworth-Howard test as originally performed.

We have also attempted recently a further test of the Albright theory which is part of a programme of investigation into the calcium-phosphorus product mechanism. Briefly, we have reduced plasma phosphate levels by means of oral aluminium hydroxide and looked for any ensuing changes in calcium levels. We argued that if the Albright theory were correct a fall in plasma phosphate produced by any means should, other things being equal, provoke the calcium-phosphorus product mechanism as from stage 2 of Fig. 1 and lead to the same consequences from then on as occur after an injection of parathormone. This however did not occur. The plasma calcium did not change significantly. We have only done this three times, but the experiments were carefully controlled and the results are we believe significant.

There is also a great deal of experimental evidence indicating that parathormone can act on bone and produce the blood electrolyte changes equally well in the absence of the kidney. This work has been reviewed most impartially by Albright and Reifenstein (1948) in their classic textbook. Stewart and Bowen (1951) have shown this more recently in especially well conceived experiments. There is also some clinical evidence that the plasma calcium level is more closely related to the action of parathormone than the phosphate level. This can be shown by plotting the levels in patients for a period before and after removal of a parathyroid adenoma. It is easily seen that the raised calcium level falls at once after the operation, usually being normal or subnormal within three to four days. The rise in phosphate is usually much slower and is more unconvincing. It is undoubtedly this closer relation to calcium metabolism which has biased clinical diagnostic methods towards a study of calcium levels and urinary excretions, rather than of phosphate. Likewise in the assay of parathyroid extracts it is the calcium raising power which has always been used as the criterion of parathormone content, and attempts to assay it by its phosphate excretion effects have been generally rejected. Barnicot (1948) has also shown a direct dissolving action on bone of a piece of parathyroid tissue grafted in close proximity to it.

There is also much armchair criticism that can be levelled at any theory that is exclusively or mainly based on a renal action. For instance, if the blood electrolyte levels cause the bone changes then there should be a correlation between blood levels and the two main clinical types of hyperparathyroidism, namely, that with and that without demonstrable bone changes. Not only is this not so but the electrolyte changes in both cases tend to be most inconsistent (hence the difficulties in diagnosis). In cases with renal disease, for instance, the blood phosphate may be normal or even raised; this should reverse Albright's scheme (Fig. 1) and lead to a phase of recovery of the bone disease. That this is not so is well shown in primary renal disease with secondary hyperparathyroidism where identical bone changes may occur even though the kidney has never been able to react in the desired fashion. It is also difficult to explain on a renal basis the oversaturation of the body fluids with calcium phosphate that is known to occur. If calcium phosphate dissolves out of bone, as Albright suggests, to maintain a disturbed calcium-phosphorus product, the result should be osteomalacia and not osteitis fibrosa.

In spite of the above criticisms of a primary renal action, the writer believes that a renal action exists and that this action is indeed, as Albright states, concerned with increasing phosphate clearance by the kidney. Only in this way can the low plasma phosphate levels so characteristic of uncomplicated hyperparathyroidism be accounted for. It is probably not just due to a direct action on the kidney of the raised calcium level consequent on osteoclastic bone resorption since a low phosphate is not usually found with the raised calcium when rapid resorption is taking place under other circumstances, e.g. after sudden immobilization or in the presence of widespread secondary carcinoma. The renal action is better considered as less important than its primary action which is that on bone. It is easier to conceive it as a teleological mechanism for lowering the calcium-phosphorus product and hence the tendency to ectopic calcification in the presence of a raised plasma calcium. It must be stressed that this secondary action is quite independent of the primary bone action since in the presence of renal damage only the latter can and does operate.

The appended scheme (Fig. 2) is put forward as representing the present state of knowledge concerning the actions of parathormone. It is not complete by any means. It ignores, for instance,

THE ACTION OF PARATHYROID HORMONE

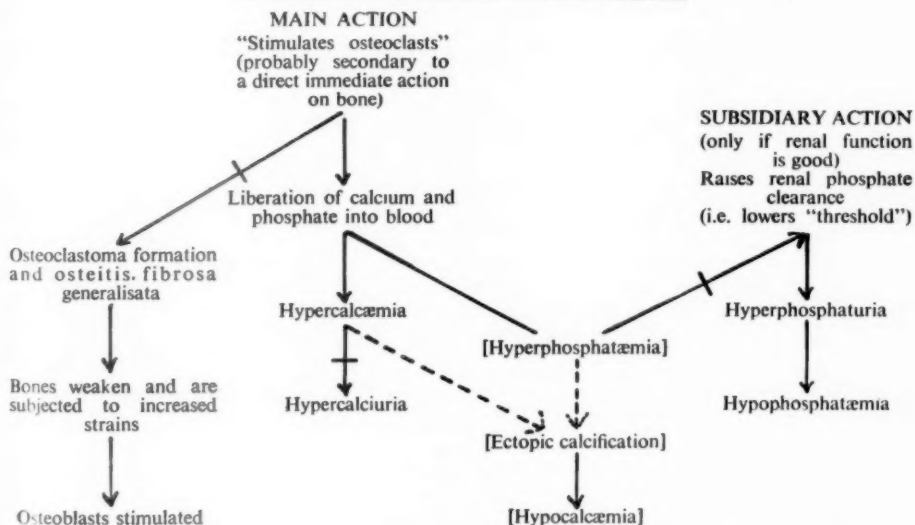


Fig. 2.—A scheme which attempts to explain most of the known actions of parathyroid hormone. The arrows marked with cross lines indicate steps not constantly present. The reason for only occasional osteoclastoma formation is not known. The renal action can only occur in cases without serious renal failure. In the presence of renal failure the events follow the dotted arrows.

Martin and Perkins' (1951) recent contribution concerning the calcium binding power of serum albumin in cases of hyperparathyroidism. It is stressed that the main problem at the moment is the preparation of a really pure hormone (or hormones). It is unfortunate that so little has been

done recently in this direction. Until this is achieved, experimental work using the crude preparation will remain under suspicion and we will continue to be largely dependent on studies taken as opportunity offers from clinical material.

REFERENCES

- ALBRIGHT, F. A., and REIFENSTEIN, E. C. (1948) *The Parathyroid Gland and Metabolic Bone Disease*. London.
 BARNICOT, N. A. (1948) *J. Anat., Lond.*, **82**, 233.
 COLLIP, J. B., CLARK, E. P., and SCOTT, J. W. (1925) *J. biol. Chem.*, **63**, 439.
 ELLSWORTH, R., and HOWARD, J. E. (1934) *Bull. Johns Hopk. Hosp.*, **55**, 296.
 MARTIN, N. H., and PERKINS, D. J. (1951) *Lancet*, ii, 295.
 MILNE, M. D. (1951) *Clin. Sci.*, **10**, 471.
 STEWART, G. S., and BOWEN, H. F. (1951) *Endocrinology*, **48**, 568.

Dr. P. M. F. Bishop:

Hyperparathyroidism

The Effects of Excessive Parathyroid Activity (see Fig. 1)

(1) *On the kidney and blood.*—According to Albright the primary site of parathyroid activity is on the excretion of phosphates by the renal tubules. Excessive activity leads to relative failure to reabsorb phosphate. This gives rise to excessive excretion of phosphate in the urine. The level of inorganic phosphate in the blood therefore diminishes. A homeostatic constancy in the product of phosphate and calcium is maintained whenever possible, and consequently as the phosphate level drops the serum calcium level rises. The first reaction to this excess of blood calcium is to excrete it through the kidney. This constitutes the “*biochemical syndrome*” of hyperparathyroidism, namely phosphaturia, low serum phosphate, hypercalcaemia, and excessive excretion of calcium in the urine. This, in itself, is almost diagnostic of hyperparathyroidism. Theoretically this biochemical syndrome could be established without any pathological or clinical manifestations, and if the condition were corrected at this stage, no harm would be done. It is however almost impossible to detect the metabolic deviation during this phase.

What happens next depends to some extent on how much calcium is available from other sources to maintain the high serum calcium level which is required to compensate for the low inorganic phosphate level in the blood. If the diet contains reasonable quantities of calcium it is, at this stage, unnecessary to call upon the calcium reserves in bone. Calcium continues therefore to be maintained at high levels in the blood, and to be excreted in large quantities by the kidney. Sooner or later this must lead to pathological changes in the kidney. Calcium becomes deposited in the collecting tubules and gives rise to *nephrocalcinosis* or else renal calculi are formed—*nephrolithiasis*. In any case the effort to excrete such excessive amounts of calcium leads to polyuria, because additional quantities of water need to be excreted, and this in turn produces thirst—“*calcium diabetes*”. Indeed at this stage the erroneous diagnosis of diabetes insipidus is often made. During this phase the patient may also complain of a variety of non-specific symptoms such as excessive fatigue, muscular weakness, anorexia, vomiting, constipation, and may be found to suffer from peptic ulceration. These are all probably due to the effect of the high serum calcium level causing atony of skeletal and smooth muscle. This constitutes the “*renal syndrome*”. It may progress and produce sinister and irreversible effects which will eventually cost the patient his life, without any of the so-called classical bone lesions of hyperparathyroidism. This phase of the disease has been labelled “hyperparathyroidism-without-bone-disease” by Fuller Albright. However excusable it may be to fail to recognize the symptomless “*biochemical syndrome*”—and in these days of exhaustive laboratory investigations one might make a good case for routine serum calcium estimations where the presenting symptoms of fatigue and vague digestive disturbances tax the diagnostic acumen of the clinician—the existence of renal stones should provide the necessary clue. 5 per cent of all cases of renal calculi at the Massachusetts General Hospital were associated with hyperparathyroidism, and if all physicians, surgeons and genito-urinary surgeons would insist on a serum calcium estimation in all cases of renal stone the incidence of associated hyperparathyroidism might well be found to be much greater. The importance of this cannot be too strongly emphasized. The prime cause of death in cases of hyperparathyroidism is renal failure, and the prognosis of any individual case depends on how soon the renal condition is recognized and treated.

(2) *On the bone.*—Hyperparathyroidism-with-bone-disease sometimes follows, and is sometimes superimposed upon the renal phase of the condition. It largely depends on the calcium intake and this may be determined by the actual concentration of the calcium in the diet, or the efficiency of calcium absorption from the gut. If adequate supplies of calcium are not available from the gut then other sources, such as bone, are called upon to supply the calcium to maintain the artificially high levels of serum calcium, demanded by the constant drain on the serum inorganic phosphate. It would perhaps be misleading to insist that it is extracted from bone only when all other sources of calcium have been exhausted. The two opposing theories of parathyroid function have now been partially reconciled. Albright, who maintained that the action of the parathyroid hormone was on the tubular reabsorption of phosphate, and Collip, who believed that it was concerned with

Fig. 1
ed serum
serum
fibrosa
clastom
phosph

that be
in the
inabilit
osteitis
all sort
and the
develop
(1) The
charac
this evi
to cate
osteobla
the bio

the mobilization of calcium from bone, have compromised their differences, and we are now asked to believe that the hormone has two functions—to control the urinary excretion of phosphate, and accelerate the turn-over of bone formation. We may suppose that sometimes this function is secondary to the renal function, so that in some cases the renal syndrome antedates the "osseous syndrome". In other cases these functions are manifested simultaneously and bone lesions occur early in the disease. It would appear that the normal action of the hormone is to regulate the rate of bone formation—to control the rate of bone deposition by the osteoblasts, and of bone resorption by the osteoclasts; but over-activity of the hormone seems to accelerate the process in such a way

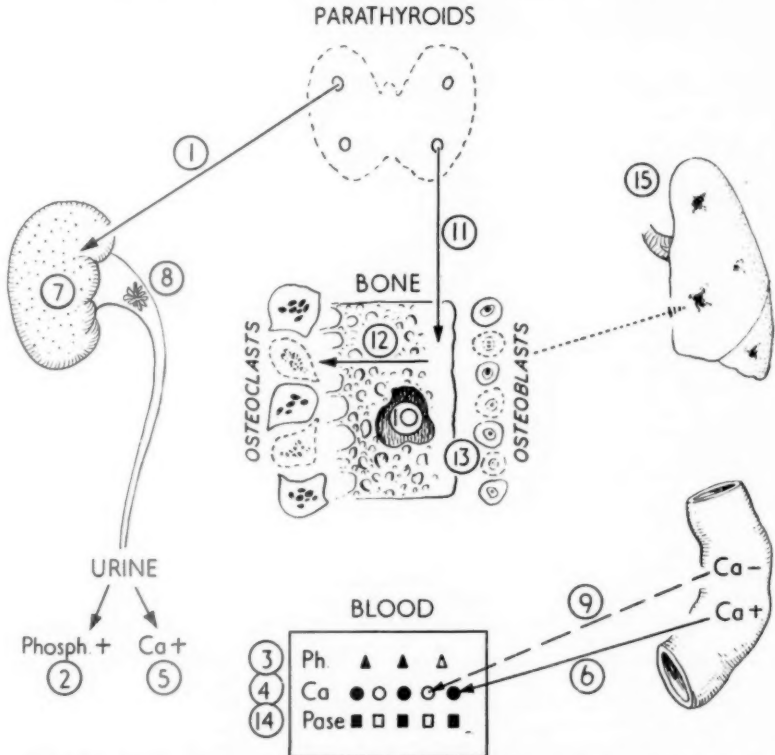


FIG. 1.—The effects of hyperparathyroidism: 1. Failure to reabsorb phosphate. 2. Phosphaturia. 3. Diminished serum phosphate. 4. Increased serum calcium. 5. Calciuria. 6. Adequate calcium intake maintaining high serum calcium. 7. Nephro-calcinosis. 8. Nephro-lithiasis. 9. Inadequate intake of calcium, leading to 10. Osteitis fibrosa and bone cysts. 11. Hyperparathyroidism leads to mobilization of calcium from bone and 12. Osteoclastoma. 13. Bone rarefaction leads to compensatory osteoblastic activity, accompanied by 14. Raised serum phosphatase. Excessive osteoblastic activity may lead to 15. Metastatic calcification.

that bone resorption exceeds bone deposition. There is evidence of the prominence of osteoclasts in the osteoclastomata, or giant-cell tumours of the skull, and other bones. There is evidence of inability to maintain the normal bone structure, and areas become fibrous, instead of bony: *osteitis fibrosa*. Some areas actually become cystic. The weakened bony structure bends easily and all sorts of bizarre deformities consequently occur. Spontaneous fractures are readily produced, and the classical appearance of *osteitis fibrosa cystica generalisata* (von Recklinghausen's disease) develops. Certain manifestations are almost pathognomonic of hyperparathyroidism. They are (1) The "moth-eaten" appearance of the skull. (2) The subperiosteal bone resorption, which is found characteristically in the phalanges, and (3) the absence of the lamina dura of the teeth. But, although this evidence of bone resorption is so prominent one must not forget that there is a constant attempt to catch up with it by increased deposition of bone. There is marked increase in the activity of the osteoblasts which is manifested by a raised level of alkaline serum phosphatase, which completes the biochemical syndrome of hyperparathyroidism. Thus, though it may be difficult to detect

clinically the biochemical syndrome, or the renal syndrome, it should not be difficult to identify the osseous syndrome, and immediate treatment is called for.

Treatment.—Surgery is the only possible form of treatment. 80% of parathyroid adenomas are found in the region of the thyroid, but if the adenoma arises in one of the inferior parathyroid glands, the anlage of which arises from the third branchial cleft, the gland may migrate downwards with the thymus—it is sometimes known as the “parathymic gland”—and end up anywhere in the anterior mediastinum. It may be necessary therefore to split the sternum and explore the mediastinum to find the adenoma. If the diagnosis has been confidently made before operation the surgeon must pledge himself to find the adenoma. As Albright says “a good thyroid surgeon is not enough. The finding of a parathyroid tumour may be very simple or very difficult. The operation should not be undertaken by a surgeon who has not made a special study of the appearance and location of normal parathyroid glands, of their differentiation from small lymph nodes and collections of fat, &c. Much mischief has been done by the ‘let’s-have-a-look’ approach to the problem. There is no time like the first operation to uncover a small adenoma. Once the neck is filled with scar tissue, the problem becomes more difficult. As in all surgery the second fifty operations for any operator are much simpler than the first.” Occasionally the pathological condition is found to consist of diffuse hypertrophy and hyperplasia of all four glands instead of an adenoma of one gland. In such a case partial resection should be performed leaving 30–200 mg. of hyperplastic tissue.

Post-operative tetany may occur, especially if bony changes are prominent and there is a high alkaline phosphatase level, for it is usually due to the avidity of the decalcified skeleton for calcium—“hungry bones” tetany. Rienhoff of Baltimore recommends transplanting a portion of the adenoma into the thyroid or the sternomastoid muscle to prevent tetany in this type of case.

Hypertrophy and Hyperplasia.—Occasionally there is diffuse hypertrophy and hyperplasia of all the parathyroid tissue rather than a single or, rarely, two or more adenomata. Two types of parathyroid cells are histologically recognizable, the chief cell and the oxyphil cell. The latter contains granules. The chief cells on the other hand contain a clear cytoplasm, which may be partly or entirely vacuolated. If it is entirely vacuolated it is spoken of as a “water-clear” or “Wasserhelle” chief cell. If there is hyperplasia of these wasserhelle cells as well as the rest of the chief cells the condition is probably one of primary hyperparathyroidism and is accompanied by marked hypercalcaemia. If, on the other hand, there is no hyperplasia of the wasserhelle cells, but only of the other type of chief cell then the hyperplasia is probably secondary. *Secondary hyperparathyroidism* results from chronic hypocalcaemia and is usually due to advanced renal inefficiency with failure to excrete phosphate, so that the serum inorganic phosphate rises and the serum calcium falls. This provides a stimulus to the parathyroids to increase their activity in order to restore the normal balance by forcing the kidneys to excrete more phosphate and so raise the serum calcium level. These cases are often associated with long-standing azotemia and acidosis, and are properly referred to as “renal osteofibrosis” or “renal osteodystrophy”. Despite the low serum calcium levels the hyperparathyroidism mobilises calcium from the bone which may show marked osteitis fibrosa with cysts, bending and fractures, and because the serum calcium level keeps low the calcium is not excreted by the kidneys, but is deposited in the tissues leading to widespread metastatic calcification. The vessels especially tend to be calcified. Another cause of low serum calcium levels is inadequate absorption of calcium from the gut, owing to vitamin D deficiency or lack of calcium in the diet or inadequate quantities to meet increased demands, as in pregnancy osteomalacia. In these cases there may be extreme demineralization of bone, but without metastatic calcification.

Dr. R. R. de Mowbray:

Hypoparathyroidism

Hypoparathyroidism is supposed to be a rare disease. The post-operative form occurs in less than 1% of patients submitted to thyroidectomy, under optimum conditions. Idiopathic hypoparathyroidism is thought to be rarer still. Only 50 or 60 proven cases have been reported in the literature. The majority of these are referred to in the articles by Drake *et al.* (1939) and Jordan and Kelsall (1951). A considerable number of other cases of idiopathic tetany have been recorded, but these are not sufficiently well documented to enable us to establish the diagnosis. Of the proven cases of idiopathic hypoparathyroidism in the literature, only 3 have been reported from this country, yet we have seen 4 cases within the past two years at Guy's Hospital and other hospitals in the South East Region. The unexpected way in which these cases have presented suggests that more cases might be found if the clinical picture were more generally familiar. The following account is based on an analysis of the cases already reported in the literature, and of the four cases of which we have recently had experience in our group. A fuller account and bibliography will be published elsewhere (de Mowbray, Llewellyn-Smith and Symonds).

PRESENTING SYMPTOMS

Table I shows the chief ways in which hypoparathyroidism may present.

Tetany is by far the commonest presenting symptom, but it is extremely variable in nature and severity, and may easily be mistaken for other conditions (Table II). *Epilepsy* is a remarkably

commo
impres
for mo
unsusp
carpop
vulsion
precipi
to nor

Trop
genera
may be
and gr
idiopat
with n
et al.

Teet
dental
ridging

Cata
as an
been c

In c
the dir
tinued
tetany,
mainly
and su
1941;

The
4 to 5
to 10
severit
the lev
very n
alkalin

Calc
the bas

Bon

ELC

ELC

altera

TABLE I.—PRESENTING SYMPTOMS IN 57 CASES OF IDIOPATHIC HYPOPARATHYROIDISM

Symptom	Number of Cases	Percentage
Tetany	40	70%
Epilepsy or generalized convulsions	24	42%
Laryngeal spasm	5	9%
Ectodermal lesions	6	11%
Failing vision due to cataracts	6	11%

TABLE II.—MANIFESTATIONS OF TETANY

Paræsthesiæ	Bronchial spasm
Cramps	Dysphagia
Pains in the limbs	Dysarthria
Stiffness or tightness in the muscles	Pyloric or intestinal obstruction
Carpopedal spasms	Cardiac irregularities
Generalized convulsions	Raynaud's phenomenon
Laryngeal spasm	Muscular palsies

common presenting feature. On reading the case reports in the literature, one is continually impressed by the number of cases (including post-operative ones) in which the patient was treated, for months or years, as a victim of idiopathic epilepsy, the true nature of the disease remaining unsuspected until other features developed. Either major or minor seizures may be found. Though carpopedal spasms may in themselves be mistaken for focal epileptic attacks, the epileptiform convulsions are often independent of the carpopedal spasms in time of onset. Yet the epilepsy is clearly precipitated by hypocalcæmia, since the fits cease to occur when the serum calcium level is restored to normal.

Trophic changes.—Skin, hair and nails: The skin may be dry, rough and scaly. The hair may be generally sparse, or there may be patchy, or rarely complete, alopecia. The eyebrows and eyelashes may become thin, and there may be some loss of pubic and axillary hair. The nails may be brittle and grooved; sometimes they are grossly deformed, or they may be shed completely. A few idiopathic cases have been reported in which the skin, nails, mouth and tongue have been infected with moniliasis (Thorpe and Handley, 1929; Severinghaus, 1942; Sutphin *et al.*, 1943; Talbot *et al.*, 1943).

Teeth: In cases in which the parathyroid deficiency arises in childhood, the formation of the dental roots, and of the enamel and dentine, may be interfered with, and the enamel shows transverse ridging.

Cataracts: These may occur in tetany from any cause. In hypoparathyroidism, they may develop as an early feature, even in the absence of recognized symptoms of tetany, or after the latter have been controlled by treatment.

MENTAL CHANGES

In chronic cases, anxiety symptoms, irritability and depression are liable to develop, probably as the direct result of prolonged hypocalcæmia, as well as the demoralization which results from continued spasms and fits. The anxiety tends to lead to hyperventilation, which precipitates further tetany. Frank psychoses of manic-depressive or delusional types, have been recorded in a few cases, mainly in post-operative ones. These usually occur within a few days to a few weeks after operation and subside within a few weeks of restoring the serum calcium level to normal (Greene and Swanson, 1941; Scarlett and Houghtling, 1944; Barr *et al.*, 1938; Eaton and Haines, 1939).

BIOCHEMICAL CHANGES

The serum calcium level is reduced, always below 8 mg. per 100 ml., and occasionally as low as 4 to 5 mg. per 100 ml. The serum inorganic phosphate level is always raised, occasionally as high as 10 to 12 mg. per 100 ml. There is no direct relation between the level of the serum calcium and the severity of the tetany. Severe tetany probably occurs more often in post-operative cases, in which the level falls rapidly to between 7 and 8 mg. per 100 ml.; whereas tetany may be absent, or at least very mild, in chronic cases, in the presence of levels as low as 5 to 6 mg. per 100 ml. The serum alkaline phosphatase level is usually normal or reduced.

X-RAY CHANGES

Calcification in the brain.—This occurs quite commonly in hypoparathyroidism, most often in the basal ganglia, but also in the cerebellum. It is distributed bilaterally and symmetrically.

Bone-density is normal or increased.

ELECTROCARDIOGRAPHIC CHANGES.—The QT interval is prolonged, as in tetany from any other cause.

ELECTRO-ENCEPHALOGRAPHY.—There may be: (a) groups of abnormally slow waves, sometimes alternating with normal rhythm; (b) spikes; or (c) typical epileptic changes (Gotta and Odoriz, 1948).

PATHOLOGICAL PHYSIOLOGY

The findings in hypoparathyroidism are most easily explained on the basis of Albright's theory, namely that the primary action of parathyroid hormone is to induce an increase in the urinary excretion of phosphorus. Parathyroid deficiency will therefore result in a diminished excretion of phosphate, leading to a rise in the serum phosphate level, and a compensatory fall in the serum calcium level, since the blood is fully saturated with calcium and phosphate ions; any further rise in phosphate concentration will therefore lead to supersaturation of the blood, and an increase in deposition of bone-salt (Albright and Reifenstein, 1948). In our experience, the administration of parathyroid hormone to patients with hypoparathyroidism invariably leads to a marked increase in urinary phosphate excretion.

PSEUDOHYPOPARTHROIDISM

This is a congenital disorder, first described by Albright *et al.* (1942), which consists of three independent, and probably genetic, disturbances:

- (1) An abnormal peripheral resistance to the action of parathyroid hormone, resulting in all the manifestations of hypoparathyroidism.
- (2) A dyschondroplasia, resulting in dwarfism and in shortening of some of the metacarpals and metatarsals.
- (3) A tendency to metaplastic formation of bone in the soft tissues (Elrick *et al.*, 1950).

Only some 17 cases have so far been reported in the literature, and only one of these from this country (Bishop and de Mowbray, 1951). In such a case, the administration of parathyroid hormone usually fails to induce a significant increase in the excretion of phosphate in the urine.

TREATMENT

Parathormone has no place in the treatment of hypoparathyroidism. In the acute post-operative condition, symptoms can be controlled by means of calcium salts, by the intramuscular, intravenous or oral route.

In chronic cases, parathyroid hormone has 4 disadvantages:

- (1) It is expensive—
- (2) It has to be given by injection—
- (3) It is liable to give rise to reactions—
- (4) It leads to antihormone formation—and therefore begins to lose its effect after a few weeks of continual administration.

The irradiated ergosterol derivatives are equally effective in true hypoparathyroidism and in pseudo-hypoparathyroidism. The two preparations commonly used are calciferol (vitamin D) and dihydrotachysterol (A.T.10). Both are similar in chemical structure, differing only in so far as calciferol has a double bond between the C9 and 10 atoms.

Dihydrotachysterol more closely resembles parathyroid hormone in its action, its principal effect being to stimulate the excretion of phosphate in the urine, though it increases calcium absorption from the intestine to some extent. Calciferol acts principally upon the absorption of calcium, and has also a weak action on the excretion of phosphorus in the urine (Albright *et al.*, 1938). There is also some evidence that calciferol and dihydrotachysterol liberate calcium from bone.

The initial dose of dihydrotachysterol is usually 3 c.c. daily, and, for calciferol, from 200,000 to 500,000 or even a million units daily. The maintenance doses are usually from $\frac{1}{4}$ to 1 c.c. of A.T.10 daily or from 50,000 to 200,000 units of calciferol daily.

Dihydrotachysterol is theoretically preferable, in so far as it more closely resembles parathyroid hormone in its action. Calciferol has the advantage that it is much cheaper. An average maintenance dose of dihydrotachysterol (0.5 c.c. daily) costs approximately £1 per month, whereas a corresponding dose of vitamin D (100,000 units daily) costs only about a shilling per month.

As far as their effects in controlling the symptoms and the serum calcium level are concerned, there seems to be little to choose between them. Probably calciferol is more likely to lead to hypercalcaemia, in view of the fact that it acts predominantly upon calcium absorption and has a cumulative action in this respect. Though hypercalcaemia is a well-known complication of the use of high doses of calciferol in skin disorders, I have been able to find only one case of hypoparathyroidism in which acute hypercalcaemia with toxic effects resulted from this treatment, and the dose in this case was no higher than 300,000 units daily (Howard and Meyer, 1948). We recently had experience of another case, in a woman aged 48 years with longstanding post-operative hypoparathyroidism and hypertension, on a dose of 200,000 units daily. Acute hypercalcaemia is probably due either to an individual idiosyncrasy to calciferol or to impaired renal function. No serious effects seem to have been reported from treatment with dihydrotachysterol.

The Sulkowitch reaction is a useful practical guide to treatment, but is not sufficiently reliable in itself. We have found it necessary to ask for repeated estimations of the serum calcium level. The serum calcium level may be low, when the calcium reaction in the urine is apparently optimal, and, in the case of acute hypercalcaemia of which we recently had experience, there was no excess of calcium in the urine.

Never
and tha
and see
increase
The t
readju
problem
We d
phosph
Lyall, I
accuracy
tent of f
Nor c
variable

Hypo
however
and spas
associat
quarters
onset of
convulsi
The n
well to c
stimulat

ALBRI

ANDER
BARR,
BISHOP
DE MO
DRAKE
EATON,
ELRICK
3, 19
GOTTA
GREEN
HOWAR
JORDAN
SCARLE
SEVERIN
SUTPHI
TALBOT
THORPE

Dr. A.
variation
if anythin
to be mo
was very
although

Dr. R.
side of p
on neph
be produ
there fol
readers c
without
The d
disturbin
habits m
times, S
months v

Nevertheless, the Sulkowitch reaction has the great virtue that the patient can carry it out himself, and that a heavy calcium precipitate will warn him to reduce the dose, or to stop taking the drug, and see his physician immediately, while an absence of any precipitate will indicate the need for an increase in the dose.

The treatment of hypoparathyroidism is not always easy. Dosage may have repeatedly to be readjusted in response to infections or according to mental and physical stresses and strains. The problem is in fact comparable to that of the treatment of diabetes mellitus.

We do not consider that it is necessary to place the patients on a strict diet. A high calcium, low phosphorus diet, will restore the serum calcium and phosphorus levels to normal (Anderson and Lyall, 1939) but it is unlikely that a patient will be able to adhere to such a diet with sufficient accuracy. It is, however, advisable to avoid excess of milk, in view of the fact that it has a high content of phosphorus, as well as being rich in calcium.

Nor do we find it necessary to administer calcium salts, and it seems simpler to have only one variable to contend with when one is adjusting the dose of calciferol or A.T.10.

CONCLUSIONS

Hypoparathyroidism is generally regarded as a rare disorder. More cases might come to light, however, if the diagnosis were considered in patients presenting with paræsthesia, pains, cramps and spasms in the extremities, in cases of epilepsy, and of cataracts occurring in young people. Cases associated with trophic changes in the skin, hair and nails might be found in Skin Clinics. Three-quarters of the cases of idiopathic hypoparathyroidism reported in the literature have had their onset of symptoms in childhood, and the diagnosis should be considered in cases of infantile convulsions.

The majority of cases are not referred to endocrinologists in the first instance, but we should do well to draw the attention of our colleagues in other special departments to this condition, and thus stimulate a search for further cases.

REFERENCES

- ALBRIGHT, F., BLOMBERG, E., DRAKE, T., and SULKOWITCH, H. W. (1938) *J. clin. Invest.*, **17**, 317.
 —, BURNETT, C. H., SMITH, P. H., and PARSON, W. (1942) *Endocrinology*, **30**, 922.
 —, and REIFENSTEIN, E. C. (1948) *The Parathyroid Glands and Metabolic Bone Disease*. London.
 ANDERSON, I. A., and LYALL, A. (1939) *Quart. J. Med.*, **8**, 209.
 BARR, D. P., MACBRYDE, C. M., and SANDERS, T. E. (1938) *Trans. Ass. Amer. Physns.*, **53**, 227.
 BISHOP, P. M. F., and DE MOWBRAY, R. R. (1951) *Proc. R. Soc. Med.*, **44**, 952.
 DE MOWBRAY, R. R., LLEWELLYN-SMITH, S. H., and SYMONDS, W. J. C. (1953) *Brit. med. J.* (In the press.)
 DRAKE, T. G., ALBRIGHT, F., BAUER, W., and CASTLEMAN, B. (1939) *Ann. intern. Med.*, **12**, 1751.
 EATON, L. M., and HAINES, S. F. (1939) *J. Amer. med. Ass.*, **113**, 749.
 ELKRICK, H., ALBRIGHT, F., BARTTER, F. C., FORBES, A. P., and REEVES, J. D. (1950) *Acta endocr., Copenhagen*, **3**, 199.
 GOTTA, H., and ODORIZ, J. B. (1948) *J. clin. Endocrin.*, **8**, 674.
 GREENE, J. A., and SWANSON, L. W. (1941) *Ann. intern. Med.*, **14**, 1233.
 HOWARD, J. E., and MEYER, R. J. (1948) *J. clin. Endocrin.*, **8**, 895.
 JORDAN, A., and KELSALL, A. R. (1951) *Arch. intern. Med.*, **87**, 242.
 SCARLETT, E. P., and HOUGHTLING, W. J. (1944) *Canad. med. Ass. J.*, **50**, 351.
 SEVERINGHAUS, E. L. (1942) *Amer. J. med. Sci.*, **203**, 726.
 SUTPHIN, A., ALBRIGHT, F., and MCCUNE, D. J. (1943) *J. clin. Endocrin.*, **3**, 625.
 TALBOT, N. B., BUTLER, A. M., and MACLACHLAN, E. A. (1943) *J. clin. Invest.*, **22**, 583.
 THORPE, E. S., and HANDLEY, H. E. (1929) *Amer. J. Dis. Child.*, **38**, 328.

Dr. A. B. Anderson asked if the varying chemical picture in hyperparathyroidism could be due to variation in the length of time that this comparatively chronic disease had been present. He also asked if anything was known of the geographical distribution of hyperparathyroidism. The disease appeared to be more prevalent in America than in this country. In Glasgow, where all sorts of bone disease was very prevalent, he had only seen one case during ten years at the Glasgow Royal Infirmary, although the clinicians were looking for it, especially in patients attending the urological clinic.

Dr. R. V. Coxon: While it is true that Dr. Albright has attached great importance to the renal side of parathyroid action, it should, I think, be recalled that he did himself initiate some experiments on nephrectomized rats which demonstrated by histological criteria that direct effects on bone can be produced with parathormone, and this finding is duly mentioned in his book. Admittedly it there follows the exposition of his main thesis concerning the renal action of the hormone, but readers of the book are warned in the preface that the writer's hypotheses are subject to change without notice (Albright and Reifenstein, 1948).

The divergent results obtained with injections of parathormone in normal human subjects are disturbing and raise the possibility that some long-term adaptive response to variation in dietary habits may perhaps play a part in accounting for discrepant effects in different centres at different times. Such adaptive changes were noted in studies on calcium metabolism extending over many months which have been conducted by Nicolaysen (1952) in Oslo. Likewise, dietary dissimilarities

are invoked by Snapper (1949) in explanation of the variable incidence of the different clinical types of hyperparathyroidism in different parts of the world.

REFERENCES

- ALBRIGHT, F., and REIFENSTEIN, E. C. (1948) *The Parathyroid Glands and Metabolic Bone Disease*. London.
 NICOLAYSEN, R. (1952) Lecture delivered at Oxford.
 SNAPPER, I. (1949) *Medical Clinics on Bone Disease*. New York.

Dr. D. N. Baron: I wish to describe two unusual cases of hypoparathyroidism that we have been investigating. (Some investigations since the meeting are now included.)

I. HYPOPARATHYROIDISM WITH SUCCESSFUL PREGNANCY

Mrs. E. S., aged 27 years.

	Serum Ca mg./100 ml.	Serum P mg./100 ml.
11.1.52: Graves' disease: thyroidectomy	8.6	
Four hours post-operatively—tetanic symptoms	5.8	6.0
14.1.52: After treatment with A.T.10 and calcium salts	7.5	
11.2.52: Tetanic symptoms after failing to continue treatment (calcium lactate and vitamin D). Two months pregnant	4.5	
Immediate treatment with A.T.10 and maintained on 5 grammes calcium gluconate and 100,000 units of vitamin D three times daily	7.0	4.7
8.9.52: No symptoms. Birth of baby by normal delivery. Maintained on same treatment with vitamin D and calcium gluconate. Has	8.0	4.2
6.10.52: no symptoms except feeling slightly twitchy at times	7.0	
20.1.53: Very well: treatment as before	9.7	
8.9.52: <i>Baby:</i> apparently normal at birth, with no clinical or radiological evidence of calcium deficiency. Serum alkali reserve 13 mEq./l.	7.6	7.8
9.9.52: Given 2 grains calcium lactate three times daily for ten days	7.1	
12.9.52: Quite well and staying well. Serum alkali reserve 28 mEq./l.	10	7.3

II.—LONG-STANDING HYPOPARATHYROIDISM WITH A CHANGE IN RESPONSE TO VITAMIN D LEADING TO HYPERCALCAEMIA

Mrs. F. P., aged 53 years.

	Serum Ca mg./100 ml.	Serum P mg./100 ml.	Serum alk. phosphatase K-A units
Thyroidectomy for Graves' disease performed in 1930. Had had intermittent symptoms ever since, occasionally frank tetany, and has never felt really well. Treated with varying doses of calcium gluconate, vitamin D, and A.T.10 (for a short period in 1940): seen monthly for control.			
7.6.51: No overt symptoms. Being treated with calcium gluconate 3 grammes, and vitamin D 3,000 units, three times daily	9.4	5.1	4
16.5.52: Mild tetanic symptoms. Calcium gluconate increased to 4 grammes, and vitamin D to 20,000 units, three times daily	7.3	5.0	4
25.9.52: Does not feel very well	6.9	4.3	3
2.10.52: Mild tetanic symptoms. Taken off calcium gluconate; vitamin D increased to 100,000 units three times daily			
9.10.52: No symptoms. Treatment unchanged	8.9		
21.10.52: Symptoms of extreme lassitude and malaise; nausea, vomiting and pains in the stomach: headaches and marked giddiness; considerable thirst and dryness of the mouth. Treatment stopped	14.1		
23.10.52: Feels better. Has been drinking 5 pints of water a day. Still weak, and has some thirst and dryness of the mouth, and a little vomiting. Blood urea 62 mg./100 ml.	14.6	3.8	3
30.10.52: Feels better than she has done for many years. Blood urea 40 mg./100 ml.	11.1	3.1	4
5.1.53: Very well. Having 15,000 units of vitamin D daily	9.8		

Comment.—Case I shows that a patient may go through pregnancy, whilst in a state of chronic hypocalcaemia due to incomplete correction of her hypoparathyroidism, without apparent ill-effects

to herself during pregnancy. Case I carefully

Dr. C. with the that the from the where the to duration I do not The main rare disea 7 cases p to us in t hospitals I enter previous October injections I was i unexpect other. W that the p of calcife dose is n with calc I have A.T.10 in maintena standard least a ba strength. of A.T.10

Male Pse Shorth and there a twin— developed somewhat length. C abdomen Blood twenty-for She ha girl of 17 are entire herself wi Laparo the corre resembling that it wa testes. B broad fol uro-rectal almost lig attach men to form t

to herself or her child. It remains to be seen whether the dosage of vitamin D which was insufficient during pregnancy will restore the serum calcium and maintain a normal level.

Case II shows the rapidity with which hypercalcaemia may develop, and the need to control carefully any change in treatment of a case of hypoparathyroidism.

Dr. C. E. Dent, in reply: There is good evidence that the amount of renal failure present varies with the length of time the disease has been present. This changes the chemical picture to the extent that the blood phosphorus is higher than expected and the hypercalciuria reduced, apart, of course, from the other better-known signs of renal failure. The main diagnostic difficulty arises in cases where there is only a minimal rise in blood calcium (11.5 mg. % or so). I do not think this is related to duration of the disease.

I do not think there is any reason to believe yet in a geographical distribution of hyperparathyroidism. The main factor in the frequency of diagnosis is that clinicians should be looking for it. It was a very rare disease in University College Hospital before 1949. In the last two to three years we have had 7 cases proved at operation with another almost certain one waiting to come in. 6 of these 8 came to us in the ordinary way through our out-patient departments, the other 2 were referred from other hospitals with the diagnosis already suspected.

I entirely agree with Dr. Coxon's remarks. Dr. Albright has recently cast doubts about his previous views on the renal action of parathormone (Address to New York Academy of Medicine, October 6, 1952: "Hormones and common sense"). I think the divergent results with parathormone injections are more likely to be due to differences in the extract. This is very crude indeed.

I was intrigued that Dr. Baron has noted signs of vitamin-D intoxication coming on rapidly and unexpectedly. Dr. W. R. Trotter and I recently encountered 4 such cases within a short time of each other. We have been quite unable to account for this coincidence. The manufacturers are insistent that the product is stable and adequately standardized. We have recently recovered entire particles of calciferol tablets from the stools of a patient being treated with large doses. It may be that the dose is not always absorbed. Sometimes the tablet is made up, without any indication on the label, with calcium phosphate which probably increases its action.

I have used both A.T.10 and calciferol. A point not usually stressed is the more rapid action of A.T.10 in elevating the blood calcium. This makes it easier to use in determining the correct maintenance dose of a new patient. It is, however, not a pure chemical substance and has to be standardized biologically. It is our strong impression that batches vary in potency. In one case at least a batch was clearly proved (and confirmed by the manufacturers, who recalled it) to be below strength. Even more embarrassment was caused us on the two recent occasions when the supply of A.T.10 completely dried up for no stated reasons.

[November 26, 1952]

Male Pseudohermaphroditism.—C. N. ARMSTRONG, M.D., F.R.C.P., D.P.H.

Shorthand typist, aged 17 years, referred to hospital on 22.4.52 because she had never menstruated, and there was a complete absence of pubic and axillary hair, but normal breast development. Patient a twin—other twin died *in utero*. Family history of late menarche. Normal stature with well developed breasts, normal blonde head of hair (Fig. 1). No axillary or pubic hair, and skin generally somewhat hairless. Vulva infantile, but otherwise appeared normal. Vagina only half an inch in length. On rectal examination, no internal female organs palpated. No abnormal signs heart, lungs, abdomen, and C.N.S.

Blood pressure 130/90. Urine normal. X-ray sella turcica normal. 17-ketosteroids 8.9 mg. per twenty-four hours.

She has the mental attitudes of a girl. Socially and occupationally, the adaptation is that of a girl of 17 of rather above average intelligence. Sexually, she is a little immature, but her inclinations are entirely female. She has had girls' toys, has female daydreams, reads love stories, and identifies herself with female fictional and film characters—she hopes to marry and is fond of babies.

Laparotomy: There was no uterus, but a broad fold of peritoneum running across the pelvis in the corresponding position. On the left side, lying on the psoas muscle, was a gonad anatomically resembling a testis. On the right side, a similar structure was found, but more inferiorly placed so that it was lying right at the internal ring. The arrangement was entirely consistent with undescended testes. Both inguinal regions were bimanually palpated, and no swelling noted in either groin. The broad fold of peritoneum running across the pelvis is the transverse pelvic fold, a remnant of the uro-rectal septum or genital fold, and its attachment to the inguinal fold (gubernaculum) appears almost ligamentous, and may well have been a factor in checking the descent of the testis. Such an attachment as this occurs in the female from the lateral aspect of the body of the uterus to the ovary to form the ligament of the ovary (Fig. 2).



FIG. 1.—Male pseudohermaphrodism, showing external female appearance.

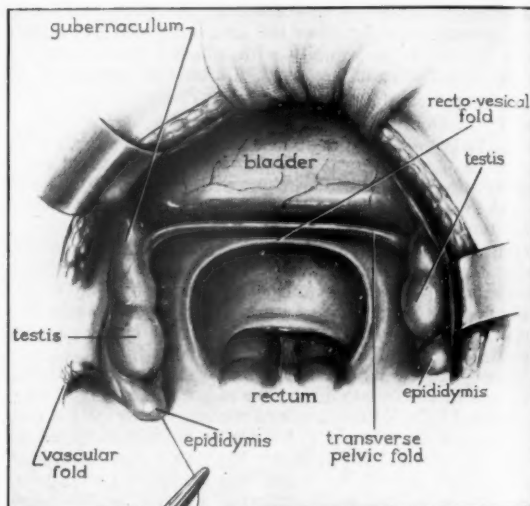


FIG. 2.—Drawing illustrating appearance of pelvis at laparotomy showing internal male gonads and absence of female organs.

D. P. Hammersley

Histology.—Material from each gonad was identical histologically, and consisted of testicular tissue. There were numerous immature seminiferous tubules which showed no evidence of spermatogenesis. Numerous and increased numbers of interstitial cells were present.

The legal determining factor in intersex cases is the anatomical structure of the gonad independent of the social or sexual inclinations or external appearance of the subject. In this case, therefore, the legal sex is male, and although one would have no hesitation in defending this patient's desire to continue living as a female, the clinical problem does arise as to how far a surgeon is justified in carrying out a plastic operation to make a vagina which, in this case, has already been requested.

Vitamin-D Resistant Osteomalacia Associated with Neurofibromatosis.—B. E. C. NORDIN, M.D., and RUSSELL FRASER, M.D., F.R.C.P.

The patient was a 33-year-old woman who was first seen in June 1952, when she complained of generalized bone pains. She had developed kyphoscoliosis in infancy, which had been progressing ever since, had had rickets as a child, and had been excessively liable to fractures since the age of 20. However, she had been ambulant and fit for light work until about two years before the present admission but had been bedridden for the last nine months, mainly on account of bone pain. Her father and a brother (both dead) had had kyphotic deformities, and her mother had had multiple neurofibromatosis.

The patient weighed just under 4 stone and was 4 ft. in height. She had a very severe dorsal kyphoscoliosis with angulation in the midthoracic region, and a false joint with right angle deformity of the right forearm. There were multiple neurofibromata on the trunk, face and limbs.

Radiography revealed thin bones, a tri-radiate pelvis and typical Milkman fractures in the scapulae and the right femur, and fractures in the left clavicle, the right second metacarpal, the right ulna and elsewhere (Fig. 1). The only metabolic abnormality was a low blood phosphate (1.5 mg. %) associated with a relatively high urinary phosphate excretion (nearly 500 mg./24 hours). During the first five days in hospital she rejected all her food and her blood phosphate fell to zero.

Investigation did not reveal the cause of her osteomalacia. Steatorrhoea was excluded by a normal fat balance; Fanconi's syndrome by the absence of abnormal amino-acids and glucose in the urine; renal tubular acidosis by her ability to excrete a highly acid urine (pH 4.5–5.0) containing 50 mEq. ammonia in twenty-four hours after three days on an acid load of 100 mEq. daily. She therefore fell into the category of vitamin-D resistant osteomalacia, and, as expected, her clinical condition and X-ray appearances (Fig. 2) responded slowly but unmistakably to large doses of vitamin-D (50,000 units daily, later raised to 250,000). There was also a rise in blood calcium and phosphate until the former was above and the latter within the normal range (Fig. 3).

FIG. 3.—
both when
after withdr



FIG. 1.—X-ray on admission showing tri-radiate pelvis, Milkman fractures of right femur and right ilium and fractures in the pubic rami.



FIG. 2.—X-ray after three months of vitamin-D therapy showing callus formation at site of fractures.

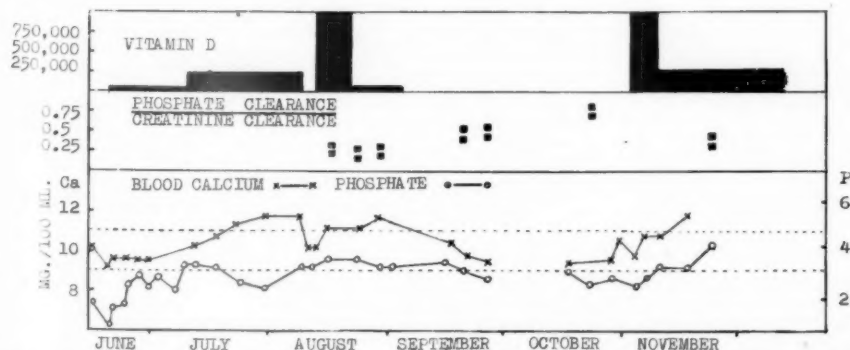


Fig. 3.—Shows the steady rise in blood phosphate and calcium in response to vitamin-D and the fall in both when vitamin-D is withdrawn. Note also the rise in phosphate clearance : creatinine clearance ratio after withdrawal of vitamin-D.

Comment.—The main interest in this case attaches to the aetiology of the condition. The family history is suggestive of a hereditary factor and the lesion is clearly a congenital one. The primary defect in "vitamin-D resistance" is still unknown, and the only hypothesis which has been put forward is that of Fanconi and Girardet (1952) and Dent (1952) that there is a primary renal phosphatic leak; Fanconi has coined the term Phosphate Diabetes to describe the condition. On the other hand Albright and Reifenstein (1948) believe that the low blood phosphate and high phosphate clearance may be due to secondary hyperparathyroidism.

Whatever the cause of the phosphate leak in our patient, it certainly responded to vitamin D. The phosphate : creatinine clearance ratio was just within normal limits (0.2–0.3) after three months' therapy, and rose to 0.75–0.85 when vitamin D was withheld for six weeks. The severity of the leak can also be gauged from the fact that the blood phosphate fell to zero after five days' starvation.

REFERENCES

- ALBRIGHT, F., and REIFENSTEIN, E. C. (1948) *The Parathyroid Glands and Metabolic Bone Disease*. London.
 DENT, C. E. (1952) *J. Bone. Jt. Surg.*, **34B**, 266.
 FANCONI, G., and GIRARDET, P. (1952) *Helv. paediat. acta*, **7**, 14.

Cushing's Syndrome Due to Adrenal Cortical Tumour.—J. M. STOWERS, M.R.C.P. (for Professor M. L. ROSENHEIM, F.R.C.P.).

Miss B. W., aged 34, had been very healthy until February 1951, when she developed amenorrhœa and personality changes with impairment of her memory and general indifference. These changes she ascribed to an unusually early menopause and she did not consult a doctor. In August 1951, her voice became husky and deeper in pitch and she gained 14 lb. in weight in six months. The increase in weight was distributed over the trunk, neck, shoulders and face, sparing the limbs. After Christmas 1951 there was a more rapid development of symptoms. Coarse dark hairs grew on the face and a finer growth appeared on the limbs and abdomen. The scalp hair became thick and greasy and acne developed on the face and chest. Shortly before coming to University College Hospital her periods had returned and she thought her physical strength was increasing.

On examination.—Characteristic appearance of Cushing's syndrome with buffalo obesity, round, red, hairy face, relatively thin limbs and purplish striae over the flanks. B.P. 140/100. All systems normal, but Professor W. C. W. Nixon considered there was some enlargement of the clitoris.

Blood count normal. Low total eosinophil counts. Plasma cholesterol 150 mg./100 ml.

Androgens: Neutral 17-ketosteroid excretion:

1952: March	60 mg./day	
April 4	104	less than 10% β fraction.
11	54	35% β Patterson test positive.
23	66	18% β

Dr. H. Pond (King's College Hospital) analysed the urinary 17-ketosteroids chromatographically on an alumina column: there was (1) a high total, (2) a large proportion of the β fraction and (3) a normal androsterone : etiocholanolone ratio.

Carbohydrate metabolism: Occasional slight glycosuria associated with a normal blood sugar. Oral and intravenous glucose tolerance tests normal.

Urinary 11-oxy steroid excretion (April 16) 0.66 mg./day (normal 0.15 to 0.4) (modified Talbot method).

Mr. I. E. Bush analysed the urinary 11-oxy steroids chromatographically. There was a considerably increased output especially of the fraction measured after immediate acid hydrolysis.

Electrolytes: Serum chlorides 93 and 100, sodium 133 and 143, potassium 3.6 and 4.2; mEq./l. plasma CO_2 combining power 28 mEq./l. Serum Ca 8.8 mg./100 ml. Sulkowitch test on urine strongly positive.

Radiology: Skull normal. I.V.P.: Good concentration of the dye. The left kidney appeared to be depressed and rotated by a mass lying on its superomedial aspect. Chest normal. Long bones and spine: no evidence of decalcification. Abdomen: large rounded abnormal shadow under the left diaphragm.

Soft tissue pneumatography (Dr. C. J. Hodson): large discrete round mass lying in the left paravertebral gutter.

There was good evidence for the existence of a large tumour, probably malignant (17-ketosteroid results), of the left adrenal gland. The tumour appeared to be secreting androgens, glucocorticoids and possibly some mineralo-corticoids.

Operation (Mr. W. R. Merrington) 25.4.52: The patient was prepared with pre- and post-operative ACTH and cortisone and supplementary potassium chloride by mouth. A metabolic balance study

was made
the opera

Left ki
adrenal in
and diaph
for histol
then ph
steroids s
in saline
this eluat
hydroxyc
quantitat
also exam
the pre-o
no tender

Histolo
ponceau-
Rapid

Urinary
mg./day.

Absolu
(May 14)

One we
oily. The
body hair
became n
Physicall
state and

Hypopara

L. S., a
was follow
and this
Middlesex

Lesions
ill twelve
calcium g
on vitam

A num
sister suff
Impetig
on an ery
The cond
or without

Functioni

Liver
M.R.

L. K.,

History
occurred.

Operati
seen stud

Immed

In the
gradually
to hospita
Blood sup

4.6.52;
glucose d

was made with the assistance of Dr. J. D. Nabarro from eight days before to fourteen days after the operation.

Left kidney incision: Very vascular spherical tumour removed leaving small piece of normal left adrenal in situ. Vascular connexions were severed between the tumour and the renal vessels, aorta and diaphragm, a small hole being made inadvertently in the latter. After removing a little of the tumour for histology the remainder was perfused with warm heparinised saline through a small artery and then plunged into iced saline before it was perfused with blood by Mr. Bush in order to identify steroids secreted into the perfusate. Operation swabs containing blood from the tumour were eluted in saline and the fluid so obtained similarly analysed chromatographically for 11-oxysteroids. Both this eluate and the blood perfused through the tumour were shown to contain compound F (17-hydroxycorticosterone) as the only 11-oxysteroid in identifiable concentration, and there was quantitative evidence of synthesis of compound F by the tumour. The extract of perfused blood was also examined for 17-ketosteroids by Dr. Pond who identified in it similar fractions to those found in the pre-operative urine. The patient stood the operation very well and the blood pressure showed no tendency to fall.

Histology.—Epithelial tumour of the adrenal cortex, probably of low-grade malignancy. Vines' ponceau-fuchsin taken up by some cells.

Rapid convalescence marred only by a small transient left pleural effusion.

Urinary 17-ketosteroids.—April 27, 1952, 32 mg./day; May 21, 1 mg./day, no β fraction; June 17, 3.5 mg./day.

Absolute eosinophil count one week after operation 230 per c.mm. Urinary 11-oxysteroids (May 14) 0.27 mg./day (normal 0.15 to 0.4). Plasma electrolyte levels normal.

One week after the operation the patient's voice was thought to be higher pitched and the skin less oily. The acne disappeared. The facial hair was removed mechanically and did not regrow, and the body hair gradually receded over the next two or three months. The weight distribution rapidly became more normal in spite of little change in total weight. B.P. 110/75 (June). Periods normal. Physically a little less strong than before her operation. The patient returned to her normal mental state and is now working full time.

Hypoparathyroidism Complicated by Impetigo Herpetiformis.—D. G. FERRIMAN, D.M., M.R.C.P.

L. S., a woman aged 40. June, 1951: a partial thyroidectomy for a non-toxic adenomatous goitre was followed by mild tetany. One month later a rash appeared in the pubic and sub-mammary areas, and this became generalized in September 1951, when the patient was admitted to the North Middlesex Hospital, under the care of the Dermatologist, Dr. M. Feiwel.

Lesions of impetigo herpetiformis were found. The serum calcium was 5.0 mg. %. She became very ill twelve days after admission, and her temperature rose to 106° F. She was treated with intramuscular calcium gluconate, A.T.10 and ACTH. She made a good recovery which has since been maintained on vitamin D and calcium lactate by mouth.

A number of relations are obese. Her mother and one sister have had diabetes mellitus. Another sister suffered from transient goitre.

Impetigo herpetiformis is a rare condition. The typical lesions consist of small pustules grouped on an erythematous background, but these tend to coalesce and a generalized dermatitis develops. The condition appears in normal people, but there is an important association with pregnancy, with or without tetany, and hypoparathyroidism (Beek, C. H., 1951, *Dermatologica, Basel*, 102, 145).

Functioning Malignant Islet-Cell Tumour of Pancreas. Primary Growth Removed, Metastases in Liver Seen. Recurrence of Hyperinsulinism, Treated with Cortisone.—A. STUART MASON, M.D., M.R.C.P.

L. K., male aged 36.

History.—February 1952: Attacks of unconsciousness becoming more severe until convulsions occurred. The attacks were associated with a blood sugar of 30 mg. % and were relieved by glucose.

Operation.—1.4.52: Removal of tumour in tail of pancreas (Mr. J. E. Richardson). Metastases seen studding the liver which appeared to be enlarged. Tumour and metastasis consisted of islet cells.

Immediate post-operative course satisfactory.

In the fourth week after operation there were daily morning attacks of hypoglycaemia, which gradually terminated in severe convulsive attacks (blood sugar 24 mg. %) at night on readmission to hospital (29.5.52). By adding up to 200 grammes glucose between meals attacks were minimized. Blood sugar levels varied widely (maximum 220 mg. %, minimum 36 mg. %).

4.6.52: Oral cortisone started (25 mg. six-hourly). On second day of administration additional glucose discontinued. No symptoms of hypoglycaemia occurred. Blood sugar levels varied from

180 to 68 mg. %. Dose of cortisone reduced to 12.5 mg. six-hourly on 10.6.52 but no recurrence of hypoglycaemia. Gained 5 lb. in weight in first ten days of cortisone therapy. Discharged from hospital 19.6.52.

Cortisone dose has been increased to a total of 75 mg. daily, in view of two hypoglycaemic attacks, both of which occurred after missing a meal. The patient has remained in good health eating a high protein diet. His weight has returned to normal. Liver still enlarged but more easily palpable.

Comment on post-operative progress.—This patient's pre-operative course and the histology of the tumour have been reported by Richardson and Russell (Case V, 1952). After removal of the primary growth the metastases did not produce significant amounts of insulin until one month after operation. However, severe hypoglycaemia then recurred. As ACTH and cortisone had been reported to relieve the hypoglycaemia caused by benign islet-cell tumours (McQuarrie *et al.*, 1951), it was decided to try cortisone in this case.

Cortisone raises the blood sugar by promoting gluco-neogenesis and by inhibiting the peripheral action of insulin. Brown *et al.* (1952) considered that the amount of carbohydrate formed from protein under the influence of cortisone was not sufficient to account for the alleviation of hypoglycaemia. In this case the small dose of cortisone required to prevent severe hypoglycaemia makes it very probable that it acts as an insulin antagonist. The patient has now taken cortisone continuously for twenty-five weeks and his general condition is excellent. It may be possible to prevent him dying from hypoglycaemia by continuing this treatment.

The rarity of this type of tumour makes it impossible to gauge the natural history of the disease. I can find records of 24 cases of metastasizing islet-cell tumours associated with hypoglycaemia (for review see Howard *et al.*, 1950). The tumours have occurred in patients ranging from 18 to 73 years old but the majority were found in the fourth and fifth decade of life. Most of the primary tumours were in the tail of the pancreas as in this case. The metastases always involved the liver. It is uncertain how often the metastases produced insulin. In 3 cases insulin has been extracted in large quantities from the metastases. In 4 cases the primary tumour has been resected and hypoglycaemia has recurred in 3 of these. Few patients appear to have survived more than five months after discovery of the metastases. It is not clear from the scanty data on some of these patients whether they died from hypoglycaemia or from the neoplastic process. On the other hand, patients with malignant islet-cell tumours which produced no insulin have survived up to six years after the discovery of metastases. In view of the great difference seen from case to case it is impossible to forecast the future in this patient. So far cortisone therapy has proved to be successful in alleviating hypoglycaemia but it is improbable that it is having any effect on the growth of the tumour.

Progress note (28.3.53): His weight has remained steady and his general condition good. Cortisone still controls the tendency to hypoglycaemia but the dose has had to be increased to 112 mg. daily. Minor attacks of hypoglycaemia occur at this dose if he does not eat his full diet. During the last ten weeks the liver has increased in size considerably. At the moment he is undergoing a course of deep X-ray therapy to the liver area in an attempt to control the neoplastic process.—A. S. M.

REFERENCES

- BROWN, H., HARGREAVES, H. P., and TYLER, F. M. (1952) *Arch. intern. Med.*, **89**, 951.
HOWARD, J. M., MOSS, H., and RHOADS, J. E. (1950) *Int. Abstr. Surg.*, **90**, 417.
MCQUARRIE, I., ZIEGLER, M. R., WRIGHT, W. S., BAUER, E. G., and ULSTROM, R. A. (1951) *Proc. Second Clinical A.C.T.H. Conf. Philadelphia*; Vol. II, p. 69.
RICHARDSON, J. E., and RUSSELL, D. S. (1952) *Lancet*, ii, 1054.